1 SCIENTIFIC DISCUSSION

1.1 Introduction

Renal cell carcinoma

Renal cell carcinoma (RCC), also- called renal adenocarcinoma, is a form of kidney cancer that arises from the cells of the renal tubule. RCC accounts for 90-95% of tumours arising from the kidney, and represents approximately 2% of all adult malignant tumours [1]. Over the past five years decades, the number of individuals diagnosed with RCC has dramatically[1] increased: it is estimated that the prevalence in the US has risen by 126% in this period [2]. Several factors may explain the rise including significant improvements in diagnosing due CT and MRI, but also additional factors like smoking, hypertension, obesity and diet have contributed to the rising incidence of RCC [3]. The male to female ratio is 1.5:1 [4].
RCC is the sixth leading cause of cancer death [5] and is responsible for an estimated 95,000 deaths worldwide [6]. In the past 30 years, prognosis for RCC appears to have improved. The American Society of Cancer Surveillance Research showed an increase in the 5-year survival rates from kidney cancer in the period 1992–1999 (63%) compared with 1974–1976 (52%) and 1983–1985 (56%) [7]. However there is a marked difference in outcome between early and advanced RCC. Advanced RCC is defined as metastatic, locally advanced and/or unresectable RCC. A median survival time of 6-12 months and a 2-year survival rate of 10-2-% have been estimated for patients with metastatic RCC [8]. Approximately 25% of patients have metastatic disease when RCC is first diagnosed and this number rises to 33% when those who develop metastatic spread throughout the course of the disease are also considered [8].
The main histological subtypes of RCC are clear cell, chromophilic, chromophobic, oncocytic, collecting duct carcinomas and unclassified. Clear cell Carcinoma is the most common form of renal tumour, and accounts for 70-80% of all cases of RCC [9].

Treatment of advanced RCC

The management of a patient with RCC is determined by the stage of the disease. Due to the proposed indication only the treatment of patients with advanced real cell carcinoma is described. In the last 25 years, the overall prognosis for patients with metastatic RCC (mRCC) has not appreciably improved. RCC is highly resistant to systemic therapies, including chemotherapy and radiation therapy. Although RCC tumours express receptors for estrogen, progesterone and testosterone, hormone therapy is not considered sufficiently effective [10]. A large meta-analysis (over 50 trials) revealed on average an overall objective response rate of 5.5% for chemotherapy in mRCC patients [11].
Cytokine therapy is considered a modestly effective systemic treatment of RCC that may be limited by drug-related adverse events. An overview from multiple clinical trials with IFN revealed a response rate of 12-15% for IFN [12]. A metaanalysis of 4 randomized trials provided evidence for a reduced one-year mortality (hazard ratio 0.56) with IFN treatment [12]. However, in patients with intermediate risk, this has been challenged by recent data indicating no difference in progression-free survival (PFS) and overall survival (OS) between IFN or IL-2 treatment compared to a control with medroxyprogesterone acetate (Negrier et al, 2005).
Interleukin-2 (IL-2) has been extensively studied in RCC patients, showing widely varied response rates, with relatively few complete or durable responses [13]. The toxicity profile of high-dose IL-2 includes a 4% drug-related death rate due to a capillary leak syndrome associated with severe hypotension, pulmonary edema and renal dysfunction [14]. Low-dose subcutaneous IL-2 appears to be less effective as high-dose bolus IL-2 but better tolerable [15].

A recent randomized Phase III study evaluating IFN *versus* low-dose IL-2 *versus* IFN+IL-2 *versus* medroxyprogesterone acetate in RCC patients did not show a difference in PFS or OS for any treatment arm but a less favorable quality of life and safety profile for the cytokines [16]. The combination of immunotherapy with chemotherapy, in particular 5-FU, could not demonstrate unequivocal improvement of the outcome [15].

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In summary advanced RCC remains incurable and is a serious, life-threatening condition with high unmet medical need.

Because current treatment options for patients with advanced RCC are limited, various new treatment modalities are being investigated with the aim of improving outcomes. The pathophysiology points out that the tumour growth is dependent on multiple factors, including tumour cell proliferation and the process of tumour neovascularization. Therefore the understanding of these factors is essential to develop a new drug.

Tumour cell proliferation is stimulated by signaling molecules that activate receptor tyrosine kinases (RTKs) [17, 18] including those for the epidermal growth factor (EGFR), platelet-derived growth factors (PDGFs), c-KIT and FLT3. The binding of a growth factor to its receptor activates the receptor's tyrosine kinase activity. RAS subsequently activates the RAF/MEK/ERK pathway [19]. Activated ERK translocates from the cytoplasm into the nucleus and modulates gene expression *via* the phosphorylation of transcription factors. Thus, activation of the RAS signaling pathway initiates a sequence of events that stimulate cellular growth. Constitutive activation of RAS signaling pathways occurs through overexpression or mutation of RTKs, mutational activation of *k-ras*, or mutational activation of downstream effectors of RAS such as *b-raf* [20]. EGFR is overexpressed in a subset of human lung cancer. PDGFs support the development of glioblastomas and play a role in chronic myeloproliferative cancers. Flt3 is mutationally activated in acute myelogenous leukaemia and c-Kit is activated in gastrointestinal stromal tumours. RAS mutations are present in at least 45% of all colon cancer and in greater than 90% of tumours of the exocrine pancreas [21]. Mutated BRAF (V600E) is present in a high percentage of melanomas [20].
Neovascularization is also a highly regulated process in which the proliferation of vascular endothelial cells, lymphangiogenic endothelial cells and smooth muscle cells that support new blood vessels is controlled by multiple growth factors that bind to RTKs. The growth factors involved in neovascularization include vascular endothelial growth factors (VEGFs), basic fibroblast growth factor (bFGF), and platelet-derived growth factors (PDGFs). In addition, PDGFs also support vessel stabilization through the recruitment and maturation of pericytes [22]. Moreover, bFGF and VEGF differentially activate RAF, resulting in endothelial cell protection from apoptosis [23, 24] in addition to stimulation of proliferation [25, 26], providing conditions conducive to neovascularization.
Therefore, activation of RTK signaling pathways is an important mechanism by which the majority of human tumours are stimulated to proliferate, and by which tumour associated neovascularization is initiated and stabilized.

About the product

Nexavar contains sorafenib, an antineoplastic agent that acts as protein kinase inhibitor (ATC code: L01XE05). Sorafenib inhibits tumour cell proliferation and the tumour vascularisation through activating the receptor tyrosine kinases (RTKs) signalling RAS/RAF/MEK/ERK cascade pathway.

The acronyms used during the development of the medicinal product were sorafenib (INN, USAN, JAN of the free base) coded BAY 43-9006, sorafenib tosylate (INN, USAN for the tosylate salt) coded BAY 54-9085, sorafenib tosilate (JAN for the tosylate salt).

1.2 Quality aspects

Introduction

Nexavar is presented as film coated tablets containing 274 mg of sorafenib tosylate, which corresponds to 200 mg of sorafenib, as active substance. Other ingredients are microcrystalline cellulose, croscarmellose, hypromellose, sodium laurilsulfate, magnesium stearate, water, titanium dioxide and red ferric oxide (as colorants).
The capsules are packed in polypropylene (PP) blister and sealed with aluminium foil.

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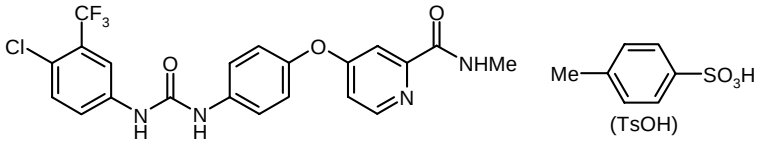
Active Substance

Sorafenib tosylate is a white to yellowish or brownish solid substance practically insoluble in water, slightly soluble in alcohols and soluble in DMSO and DMF. Sorafenib tosylate chemical name is 4-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)ureido]phenoxy}pyridine-2-carboxylic acid methylamide 4-methylbenzenesulfonate. The active substance exhibits polymorphism and it crystallizes in three different modifications (Mod I, Mod II and Mod III). It is a non-chiral molecule with the following structure:



The route of synthesis and data from structural analysis (IR, Raman, UV-VIS, ^{1}H-NMR, ^{13}C-NMR, MS, elementary analysis, X-ray structural analysis data) all support the above structure of sorafenib tosylate.

- Manufacture

Sorafenib tosylate is synthesised in six steps. The manufacture involves the synthesis of a key isolated intermediate, which is synthesized *via* three reaction steps, from the starting material. The next two steps involve the formation of sorafenib followed by the salt formation and crystallisation, resulting in sorafenib tosylate. The final step involves micronization in an air-jet mill.
The active substance is visually tested for appearance and its identity is confirmed by NIR and HPLC, and the desired modification of sorafenib tosylate (Mod I) is confirmed by Raman spectroscopy.
Batch analysis data on sorafenib tosylate micronized produced from both routes of synthesis showed that the active substance can be manufactured reproducibly.

- Specification

The specifications for sorafenib tosylate micronized and sorafenib tosylate N micronized include appearance (visual test), identity of sorafenib tosylate (HPLC and NIR), identity of modification I (Raman spectroscopy), water content (Karl Fisher), particle size distribution (laser diffraction method), heavy metals, assay on dried active substance (HPLC), related substances (HPLC and GC) and microbial purity.
Sorafenib tosylate is controlled by well-described analytical methods, which have been validated according to the ICH guidelines. The inorganic impurities are controlled by limits for sulphated ash and heavy metal. The residual solvents used in the last synthesis and purification steps are controlled in the final active substance and the specifications are within the ICH guideline on residual solvents.

- Stability

Sorafenib tosylate is a stable substance and no sign of degradation is observed after 24 months of storage under ICH long term or accelerated conditions (12 months). The active substance was found to be resistant to heat, oxidation and hydrolysis. ICH light stability studies have been performed on sorafenib tosylate in the solid state and it was concluded to be stable. When dissolved in methanol it was shown to be slightly sensitive to light. Stability data was provided on three pilot scale batches of sorafenib tosylate micronized packaged in polyamide/polyethylene (PA/PE) bags, whereas sorafenib tosylate N micronized stability data was provided on batches packaged in polypropylene (PP) bags.

The stability results justified the proposed re-test period for both sorafenib tosylate and sorafenib tosylate N.

Medicinal Product

- Pharmaceutical Development

Sorafenib tosylate tablets represent an immediate-release formulation for oral use packaged in transparent polypropylene/aluminium blisters.

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Due to the very low solubility of sorafenib in aqueous media, the tosylate salt was used in the drug product. To enhance dissolution the active substance is micronized and the particle size is tightly controlled. The permeability of sorafenib tosylate using the Caco-2 cell model indicates that it is a 'high permeability' compound.
The excipients used in the manufacture of Nexavar are all commonly used in this type of formulation. For the tablet core, microcrystalline cellulose is used as filler, croscarmellose as disintegrant, hypromellose as binder, sodium lauryl sulfate as wetting agent and magnesium stearate is utilised as lubricant. The film-coat is composed of hypromellose as the film-forming agent and macrogol as a plasticizer. Water is used as suspending liquid, and titanium dioxide and red ferric oxide as colorants. All excipients comply with PhEur monographs, except ferric oxide, which complies with Directive 94/45 EC regarding colorants in food. No materials of human or animal origin are used in the synthesis of the drug substance or in the manufacture of the drug product.
The objective of the pharmaceutical development has been to obtain a small immediate release tablet with a high amount of active substance. Sorafenib tosylate exhibited good compression characteristics and therefore a high content of drug could be used in the formulation. A wet granulation process with water as granulating liquid was found to be suitable. The content of magnesium stearate in the debossed tablet was adjusted to avoid sticking to the tabletting tools. The tablets are film coated to facilitate swallowing and to add colour.

- Manufacture of the Product

The manufacture of the finished product involves conventional processes including (1) mixing, (2) wet high-shear granulation, (3) wet sizing, (4) drying of granulate, (5) tablet compression and (6) film-coating. During process development and scale-up, the impact of manufacturing conditions on target properties of the final dosage form, such as tablet hardness, disintegration, dissolution and stability were investigated. The dissolution rate was determined to be a critical property of the product and to be affected by several manufacturing conditions. The potential for polymorphism was investigated by Raman spectroscopy and found to be unchanged.
The in-process controls were found to be adequate to the manufacture of the film-coated tablets.
The manufacturing process has been validated using three batches of the intended standard batch size. Evaluation of the batches was based on manufacturing process parameters and in-process control data. All validation batches complied with the release specifications. Batch analysis data provided shows that the film-coated tablets can be manufactured with suitable quality according to the finished product specifications.

- Product Specification

The product specifications include tests for appearance (visual method), identity (HPLC and TLC or NIR), dissolution (PhEur), uniformity of dosage units (PhEur), unspecified degradation products (HPLC), assay (HPLC) and microbial purity (PhEur).
No specified impurities are part of the finished product specification. This is acceptable since these are controlled in the drug substance and they have been found not to increase upon storage. The finished product shelf-life specifications are the same as the release specifications, exception being the water content. The specifications are considered acceptable and justified.

- Stability of the Product

Stability studies were carried out according to the ICH guideline on stability. Long-term stability data was generated on three pilot scale batches at storage conditions of 25oC/60%RH and 30oC/70%RH for 30 months. Data demonstrates that the product is stable under climate zone I/II conditions. Long-term and accelerated conditions stability data was also provided for commercial scale batches. Stress testing data was provided covering thermal and hydrolytic stress, which confirmed that high humidity can influence the properties of the finished product. Bulk stability data was also provided for one batch at 25oC/60%RH and was found to be satisfactory.
Photostability studies performed according to the ICH guideline showed that the finished product is not light sensitive.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

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Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of test carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

1.3 Non-clinical aspects

The pharmacology of sorafenib was investigated *in vitro* and *in vivo*. All pivotal toxicology studies were conducted according to the GLP standards, as claimed by the applicant.

Pharmacology

- Primary pharmacodynamics

The biological activity (IC50 values) of sorafenib was tested in biochemical assays against a selected panel of purified serine/threonine kinases and receptor tyrosine kinases. Sorafenib was active in biochemical assays against all kinases listed in Table X. Sorafenib was also tested in cellular assays (using 0.1% BSA) measuring the inhibition of the RAF/MEK/ERK pathway in human breast cancer cell line MDA-MB-231, the VEGFR-2 receptor autophosphorylation in NIH 3T3 cells expressing human VEGFR-2 receptor, and PDGF-dependent proliferation of human aortic smooth muscle cells (HAoSMC). The IC50 data is summarized in Table 1.

Table 1 - Summary of the *in vitro* profile of sorafenib

Biochemical Assay [a]	**IC50 (nM)**
CRAF [b]	6
BRAF wild-type	22
BRAF V600E mutant	38
VEGFR2	90
mVEGFR2	15
mVEGFR3	20
mPDGFR-β	57
Flt3	58
c-KIT	68
FGFR1	580
Cellular Mechanism [c]	**IC50 (nM)**
MDA MB 231 MEK phosphorylation (Human Breast)	40
MDA MB 231 ERK phosphorylation (Human Breast)	90
BxPC-3 ERK phosphorylation (Human Pancreatic)	1200
LOX ERK phosphorylation (Human Melanoma)	880
VEGFR-2 receptor phosphorylation (Human, 3T3 cells)[d]	30
VEGF-stimulated ERK phosphorylation (HUVECs)e	60
BFGF-stimulated ERK phosphorylation (HUVECs)	620
MVEGFR-3 receptor phosphorylation (Mouse, 293 cells)	100
PDGFR-β phosphorylation (HAoSMC)[f]	80
Flt-3 receptor phosphorylation (Human ITD, 293 cells)	20
Cellular Proliferation	**IC50 (nM)**
MDA MB 231 (10% FCS) [g]	2600
PDGFR-β-stimulated HAoSMC f (0.1% BSA) [h]	220

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A: Recombinant enzyme assay; b: Raf kinase activated with Lck (full length CRAF) ; c: Mechanistic cellular assays all performed in 0.1% BSA ; d: Western blot assay format with Phospho-VEGFR-2 antibody; e: Human umbilical vein endothelial cells ; f: Human aortic smooth muscle cells; g: Fetal calf serum; h: Bovine serum albumin.

Sorafenib was a potent inhibitor of CRAF and wild-type and mutant (V600E) BRAF with inhibitory concentration (IC50s) of 6 nM, 22 nM and 38 nM, respectively. Sorafenib was also a potent inhibitor of several RTKs linked to tumour progression, including Flt-3, c-Kit, VEGFR2, VEGFR3, and PDGFR-ß. Sorafenib did not inhibit MEK-1, ERK-1, EGFR, HER2/NEU, c-MET, PKA, PKB, IGFR-1, Cdk-1/cyclin B, PIM-1, GSK 3-b, CK-2, PKC-α, PKC-β, or PKC-γ at concentrations up to 10 μM.

The *in vivo* anti-tumour efficacy of sorafenib, administered as a single daily oral treatment, has been studied against non-renal tumour xenograft models using athymic mice. In each model, sorafenib was administered p.o. once a day for 9 days starting when all animals in an experiment had established tumours (tumour weight of approximately 100 mg). All doses are expressed as free base equivalents irrespective of the form of compound administered (free base or the tosylate salt). The tumour cells were implanted sc into the flank region of female athymic mice (NCr-nu/nu). Sorafenib demonstrates anti-tumour efficacy as a single agent against a broad range of human tumour xenografts including the HCT-116 (64%TGI at 30mg/kg/dose free base), DLD-1 (66%TGI at 30mg/kg/dose free base), Colo-205 (66% TGI at 30mg/kg/dose free base), and HT-29 colon tumours (21) (71% TGI at 30mg/kg/dose free base), the NCI-H460 (56% TGI at 30mg/kg/dose free base), and A549b (60% TGI at 30mg/kg/dose free base) NSCLC, the MDA-MB-231 (92% TGI at 30mg/kg/dose free base) and MX-1 (51% TGI at 30mg/kg/dose free base) mammary tumours, the MiaPaCa-2 pancreatic tumour (66% TGI at 30mg/kg/dose free base), the MV4; 11 AML (84% TGI at 3mg/kg/dose free base), LOX IMVI melanoma (52% TGI at 30mg/kg/dose free base), and the SK-OV-3 (64% TGI at 30mg/kg/dose free base) ovarian tumour. The percent tumour growth inhibition (TGI) calculated as (1-T/C)*100, where T and C represent the mean size of the treated (T) and control (C) tumours on the day after the last dose of sorafenib in each experiment.

Sorafenib exhibited anti-tumour efficacy against tumour models that express either mutated k-ras (DLD-1, Mia-PaCa-2) or BRAF (Colo-205, HT-29). Sorafenib showed efficacy against the MDA-MB-231 model that exhibits activating mutations of both genes. Sorafenib was also effective against the SK-OV-3 human ovarian tumour line that contains a wild-type ras and BRAF but overexpresses both the EGF and Her2 growth factor receptors. These receptors also signal through the RAS/RAF/MEK pathway.

The anti-tumour efficacy of sorafenib against renal tumour has been studied using female athymic mice (NCr-nu/nu). The studied xenograft models were the A498 human renal cell cancer model, the CAKI-1 human renal tumour model and the RENCA murine renal cell cancer model. In the RENCA model growth inhibition ranging from 30% to 84% was observed following oral administration of doses from 7.5 mg/kg/day to 90 mg/kg/day. Preliminary anti-tumour efficacy studies were also conducted against the A498 and CAKI-1 human renal tumour xenograft models in athymic mice. Growth of CAKI-1 tumours was not significantly (p=0.8074) inhibited by sorafenib at dose levels up to 60 mg/kg.

The mechanism of action of sorafenib was investigated *ex vivo* in multiple tumour models including HT-29, DLD-1, HCT-116, and Colo-205 colon tumour models, the MDA-MB-231 breast tumour model, and the Mia-PaCa-2 pancreatic tumour model (21). In each study, animals bearing approximately 200 mg size tumours were treated with sorafenib (30-60 mg/kg/dose) for 5 days. Tumours were then collected 3 hours after the final dose and evaluated for modulation of ERK phosphorylation by Western staining and/or by immunohistochemistry (IHC) to assess the effect of sorafenib on signaling through the RAF/MREK/ERK pathway. Tumour samples in some models were also stained with a goat polyclonal antibody against CD31 and the microvessel density was assessed by image analysis to measure the inhibition of neovascularization. An inhibition of the RAF/MEK/ERK pathway in HT-29, DLD-1, HCT-116, and MDA-MB-231 tumour models but not in Colo-205 or Mia-PaCa-2 tumours was demonstrated. Analysis of the phosphoprotein values in the MDA-MB-231 model showed that RAF/MEK/ERK phosphorylation was reduced along with six other proteins (BTK, CDK1, Ekt/BMX, MAPK1, p38, src and Zap70 (RMC-01274). Among these the CDK1 also had lower levels of phosphorylation in LOX cells *in vitro* (MRC-01275). In addition, the phosphorylation state of one protein, GSK3□ was significantly upregulated. Anti-angiogenetic effects

were evaluated *in vivo* in human xenograft models (RMC-01264). Mice with 150-250 mg HT-29, Colo-205 or MDA-MB-231 tumours were treated for 5 days with either vehicle or oral sorafenib at 30 or 60 mg/kg. Tumours were collected, sectioned, and stained with anti-CD31 antibodies. The results demonstrated that sorafenib produced 50% to 80% reduction of microvessel area (MVA) and microvessel density (MVD) in drug-treated relative to vehicle- treated HT-29 and Colo-205 tumours despite a lack of RAF/MEK/ERK inhibition in the Colo-205 tumour samples.

Three metabolites (M-2, M-4, and M-5) were synthesized and characterized for their biochemical activities against wild-type CRAF and BRAF, mPDGFR-â, mVEGFR-2, and human FLT-3. The metabolites M-2, M-4 and M-5 of sorafenib potently inhibited several receptor tyrosine kinases including VEGFR-2 (IC 50 between 7-10nM), PDGFR-β (IC 50 between 14-42nM), and Flt-3 (IC 50 between 87-170nM). In cellular assays, these metabolites inhibited the RAF/MEK/ERK pathway in tumour cells and inhibit VEGFR-2 and PDGFR signalling. Two of the metabolites, M-2, and M-5 , with IC 50 of 22nM and 46nM respectively, were more potent than Sorafenib (IC 50285nM) at inhibiting PDGF-dependent human aortic smooth muscle cell proliferation. However, Sorafenib (IC 50: 6nM) was more potent than either M-2 (IC 50: 21nM) or M-5 (IC 50: 18nM) against CRAF. For both wild-type and mutant BRAF the IC 50 was higher for M2 and M5 than for Sorafenib. Sorafenib (IC 5058nM) was also significantly more potent against Flt-3 than M-5 (IC 50: 170nM). The three metabolites (M2, M4, and M5) had similar *in vitro* pharmacological activity as sorafenib but the metabolites were present at much lower plasma levels. The most predominant human metabolite, M-2, was also evaluated *in vivo* for anti-tumour efficacy against the MDA-MB-231 xenograft model. The studies indicated that M2 was efficacious when administered orally at a dose level of 120 mg/kg on a daily schedule against s.c. MDA-MB-231 human mammary tumour xenografts in athymic mice. Lower dose levels (30 or 60 mg/kg) of M2 were not efficacious. M2 was both less potent and less active than sorafenib. A dose level of 120 mg/kg of M2 produced less growth inhibition (63%-68% TGI) than administration of 30mg/kg sorafenib by the same route and schedule of administration (80%-91% TGI). However, the degree to which M-2 contributes to the anti-tumour efficacy of sorafenib was not determined as M-2 is partially converted to sorafenib in vivo.

- Secondary pharmacodynamics

No studies were conducted to assess the secondary pharmacodynamics of sorafenib.

- Safety pharmacology programme

The safety pharmacology studies were conducted in accordance with ICH S7A and S7B [27].The only central nervous system (CNS) related effects observed in male rats were transient tremor in 2 and 3 out of 6 animals treated with 100 and 300 mg/kg. No effects on psychomotoric activity, body temperature, anti-/or pro-convulsive effect, nociceptive responsiveness or hexobarbiton induced sleeping time were observed.
For the safety of the cardiovascular and respiratory system transfected CHO cells and Rabbit cardiac Purkinje fibers were used *in vitro*. Sorafenib had no statistically significant effect on hERG current at concentrations up to 3 µM even if a tendency for inhibition was seen. At 10 µM, hERG current inhibition could not be evaluated due to unspecific effects subsequent to substance precipitation. Measurements of the action potential duration indicated a small prolongation of the APD90 , which became significant at a concentration of 10µM sorafenib. There was no toxicologically relevant effect on pulmonary function, hemodynamics, cardiac contractility and ECG in anesthetized dogs after single intraduodenal sorafenib tosylate doses of up to 60 mg/kg (corresponding sorafenib plasma Cmax approximately 3 mg/l). A transient decrease in heart rate (mean maximum of 15%) was noted at the 60 mg/kg dose but no effect on blood pressure, blood flow, P-wave amplitude, P-Q interval, QRS interval and duration of QT interval were observed.
Potential effects on diuresis, blood pharmacological parameters, blood glucose, and GI-tract were investigated in Wistar-rats after single oral sorafenib tosylate doses of 30, 100, or 300 mg/kg (corresponding sorafenib plasma Cmax approximately 3.5, 12, and 35 mg/L). There was a dose-dependent anti-diuretic effect (up to -56%) with parallel decrease in blood erythrocyte counts, hematocrit and total hemoglobin concentration, and effects gaining statistical significance at 220 mg/kg) at a systemic exposure of about 35 mg/l. No effect on blood coagulation was observed. Blood glucose levels were statistically significant decreased (maximum approximately -20% in top dose

animals) at all dose levels (fed rats) and at 73 mg/kg and 220 mg/kg in fasted animals. Sorafenib had no effect on intestinal contractions or relaxation on guinea pig ileum *in vitro*.

- Pharmacodynamic drug interactions

The ability of sorafenib (60 or 30 mg/kg/dose, p.o.) to be combined with paclitaxel, irinotecan, gemcitabine, doxorubicin, gefitinib or cisplatin was evaluated in non-clinical human tumour xenograft models.
Combinations with paclitaxel were evaluated in two mice model systems. In the NCI-H460 model, a 14-day course of treatment with sorafenib initiated concurrently with a 5-day course of treatment with paclitaxel was tolerated and had no adverse effect on the anti-tumour efficacy of paclitaxel. 10 mg/kg/dose of paclitaxel or lower was well tolerated in combination with sorafenib regardless of the sequence of administration. An evaluation of the efficacy of the combination of sorafenib administered on the q1d x 14 schedule with paclitaxel administered on either a q.d.x1 or q15d x 2 schedule was conducted in the MX-1 model. A tumour growth delay (TGD) significantly ($p<0.005$) greater in the combination than those produced by paclitaxel or sorafenib alone was observed.
Combination chemotherapy involving irinotecan (40 or 26.8 mg/kg/dose, i.p) was evaluated in the DLD-1 human colon tumour xenograft model. A multiple tumour regression of these agents was observed with concurrent administration in two separate experiments, but not with either single agent therapy.
Combination chemotherapy with gemcitabine (120 and 80 mg/kg/dose, i.p) was investigated using the MiaPaCa-2 human pancreatic tumour model. All combination therapies were as well tolerated as either single agent therapy with no lethality.
Combination chemotherapy with cisplatin (5.4 and 3.6 mg/kg/inj, i.p. on a q4d x 3 schedule) was investigated using the NCI-H23 human NSCLC tumour model. TGD produced by the combination of 60 mg/kg sorafenib and 5.4 mg/kg cisplatin (27.5 days) was significantly greater than that produced by cisplatin alone (21.4 days) at the same dose level ($p<0.04$). The TGD of the 5.4mg/kg dose level of cisplatin with the lower dose of 30 mg/kg sorafenib was not significantly different from that of cisplatin alone.
Combination chemotherapy with doxorubicin (6 and 4 mg/kg/inj, i.v.) was investigated using the MX-1 mammary tumour model. This combination of was not well tolerated, producing significantly greater dose dependent weight loss and lethality (4/10 treatment-related deaths in mice treated with the combination of the highest dose of each agent). TGD for this combination was 86%, therefore not as high in response as it was to doxorubicin treatment alone (129%) at the higher tolerated dose level of 6 mg/kg.
Combination chemotherapy with gefitinib (150 and 75 mg/kg/dose, p.o., on a q.d. x 10 schedule) was investigated using the A549 human NSCLC tumour model.
No increased toxicity or decreased efficacy of either agent was observed with this combination.

Pharmacokinetics

Pharmacokinetics of sorafenib administered as tosylate salt was investigated *in vivo* in CD-1 mice, Wistar rats and in Beagle dogs. Additionally, *in vitro* studies were performed to investigate plasma protein binding, blood cell/plasma partitioning, and drug metabolism in rodents, dogs, monkeys and human.

- Absorption-Bioavailability

The absorption and the basic pharmacokinetics following a single dose of sorafenib tosylate were evaluated in female CD-1 mice, male Wistar rats, and female Beagle dogs.
For the determination of the absorption of sorafenib in rats, bile duct-cannulated rats (n=5/group) were used. Twenty-four hours after surgery [14C] sorafenib tosylate was administered orally or intravenously to the rats at a dose of 5 mg/kg sorafenib. The absorption of sorafenib was almost complete in female CD-1 mice (78.6%) and male Wistar rats (79.2%). In Beagle dogs the absorption (67.6 %, calculated from AUCnorm values after intravenous and oral administration) and the absolute bioavailability (59.9 %) were lower than in rodents.
Maximum plasma concentrations of radioactivity between 1.5 h and 2 h after oral administration were observed in all species. After intravenous administration of [14C] sorafenib tosylate to mice, rats, and

dogs the elimination of the radioactivity from plasma occurred with similar terminal half-lives of 6.8, 8.8, and 7.3 hours, respectively. The terminal half-lives of radioactivity after oral administration were 6.1 hours in mice and 5.8 hours in dogs. In rats, terminal half-live after oral administration was longer (11.2 h) than after intravenous administration. In rats, the elimination of the unchanged compound was slower (t1/2: 9.3 h) than in the mice (t1/2: 6.5 h) and dogs (t1/2:4.3 h). The total plasma clearance in rats was 0.044 l/(h·kg) corresponding to a blood clearance of 0.049 l/(h·kg). In mice and dogs the total plasma clearance was 0.13 and 0.15 l/(h·kg) respectively. The volume of distribution at steady state ranged from 0.65 l/kg to 0.74 l/kg, depending on the species.

- Distribution

The binding of sorafenib to plasma proteins of mice (male), rats (male and female), rabbits (female), dogs (female) and humans (male and female) was investigated *in vitro* by the distribution of sorafenib between diluted plasma and between solid-supported lipid membranes according to the method of SCHUHMACHER et al [28] . The protein binding was investigated in the concentration range from 0.1 mg/l to about 10 mg/l for undiluted rat, dog and mouse plasma and in the range from 0.1 mg/l to about 5 mg/l in undiluted plasma of human and rabbits. The protein binding was about 99.5% in mice, rats and humans, 99.1% in dogs and 98% in rabbits. Human serum albumin, α-, □-globulin and the low-density lipoprotein (LDL) were the main binding proteins (fractions unbound from 1.02 to 3.55 %). In the blood of rats, dogs, and humans sorafenib was mainly equally distributed between plasma and blood cells. The plasma/blood concentration ratio was 1.12 for rats, 1.02 for dogs and 1.33 for humans. The binding of sorafenib was dependent on pH in plasma. The fraction unbound decreased to 0.165 % at pH 7.99 and increased to 1.80 % at the acidic pH 6.78.
Qualitative and quantitative distribution patterns were determined in male and female Wistar rats and male pigmented Long Evans rats by means of whole-body autoradiography. For the evaluation of the qualitative distribution patterns [14C]sorafinib was administered at a single oral dose of 10 mg/kg to male and female Wistar rats (one rat per time-point). For the evaluation of the quantitative distribution patterns [14C]sorafinib was administered at a single oral dose of 10 mg/kg to male albino Wistar rats (3 rats per time-point) and pigmented Long Evans rat (1 rat per time-point). [14C]sorafenib and/or its labeled metabolites were homogeneously distributed throughout the body, with the exception of the brain (maximum concentration of radioactivity (CEQ max) 0.391), seminal vesicles (0.363) and the compact bone (0.155). Maximum radioactivity concentration was mainly reached in most organs and tissues up to 4 hours post dosing. Blood/brain penetration was low as indicated by brain uptake less than 10 % of blood or plasma exposure. The highest exposure in terms of AUC was found in the liver (492mg-eq h/l). Similar exposure was observed in adrenal cortex (369mg-eq h/l), Harderian gland (306mg-eq h/l) and kidney outer medulla (285mg-eq h/l) and cortex (263mg-eq h/l). The rank order of the ratio organ/blood (heart) values were the following; liver (5.5) > adrenal cortex (4.3), adrenal gland (3.8), Harderian gland (2.9), pancreas (2.9), kidney outer medulla (2.7) and kidney cortex (2.6). Terminal elimination of radioactivity occurred rapidly for all organs and tissues, with half-lives mainly between 20 and 36 hours as derived from concentrations up to 7 days. Only the half-life in the skin was longer (72.8 hours).
Whole-body autoradiography was performed in pregnant Wistar rats at the 19th Day of gestation. [14C] sorafenib and/or its radiolabeled metabolites penetrated the placental barrier to a moderate extent (CEQ max ratio organ/blood: 0.988). The radioactivity was homogeneously distributed to most fetal organs and tissues, except fetal brain (CEQ max ratio organ/blood: 0.194) which contained less radioactivity. The average exposure in the fetuses reached 52 % of the exposure in maternal blood. After 24 hours, 54.4 % of the dose was present in pregnant rats, mainly in the dam, only 1.8 % of the dose could be attributed to the fetuses. Enrichments of radioactivity in the mammary glands were observed (CEQ max ratio organ/blood: 1.50).

- Metabolism

The biotransformation of sorafenib has been studied in rats, dogs, and humans *in vivo*. The biotransformation of sorafenib *in vitro* was investigated using liver microsomes, microsomes containing heterologously expressed human cytochromes or glucuronosyl transferases and rat and human hepatocytes. In vitro incubations of [14C] sorafenib tosylate with liver microsomes (protein concentration 0.5 mg/ml, 90 min) revealed two phase I prominent reactions: hydroxylation of the N-methyl group yielding metabolite M-3 and N-oxidation at the pyridine moiety yielding metabolite M-

2. Combination of both pathways led to metabolite M-1 and demethylation of sorafenib led to M-4. The percentage of radioactivity of M-2 in incubation of 16 µM [14C] sorafenib tosylate with liver microsomes was 36.4% in human, 29.4% in rhesus monkeys, 9.6% in rats and 3.8% in dogs. To identify the CYP isoforms involved in the *in vitro* phase I metabolism of sorafenib, incubations with human liver microsomes with/without CYP isoform-selective inhibitors or antibodies. CYP3A4 was found to be the responsible enzyme for phase I (oxidative metabolism) reactions of sorafenib. Sorafenib glucuronide (M-7) was identified as a minor metabolite in human plasma and was excreted into human urine (14.8 % of the dose).
From a panel of recombinant UGT enzymes UDP-glucuronosyltransferase 1A9 (UGT1A9) was identified as the main UGT isoform catalyzing conjugation of sorafenib with glucuronic acid to M-7. Kinetic parameters were determined for UGT1A9 catalyzed glucuronidation using recombinant enzyme, human kidney microsomes, and cultured human hepatocytes. High affinity to UGT1A9 was demonstrated by Km values of 5.8 µM, 8.1 µM, and 3 - 7 µM, in the respective *in vitro* model. Following incubated with cultured human hepatocytes formation of M-7 (glucuronidation) predominated at lower substrate concentrations, whereas preferentially M-2 (N-oxidation) was formed at higher concentrations of sorafenib. Intrinsic clearance (CLint = Vmax/Km) for N-oxidation was approximately 2-fold higher than for glucuronidation. Kidney tissue was also capable of forming glucuronide M-7.
In vivo, the biotransformation of sorafenib has been studied in mice, rats, dogs and humans.
Following a single oral administration, exposure to sorafenib was 71 - 73 % of the AUC of total radioactivity in the respective time interval. In contrast to man, in rat and dog plasma M-3 represented 12.1 % and 15.6 % of the AUC of total radioactivity in plasma. M-4 was found in plasma of all 3 species. Metabolite M-2 was a main metabolite in human plasma (16.7 % of AUC), but was found in small amounts in rat plasma (0.9 % of AUC) and was absent in dog plasma. The glucuronide of sorafenib (M-7) was a minor metabolite in human plasma and could not be detected in rat and dog plasma. In mice, dosed daily for 3 months, M-2, M-3, M-4 and M-5 exposures after multiple dosing were approximately 7%, 4%, 11% and 3%, respectively, of the total exposure (sum of parent and measured metabolites).

- Excretion

For the determination of absorption, excretion and mass balance of the radioactivity ([14C] sorafenib and radiolabeled metabolites) in rats and dogs the compound was administered as an intravenous bolus injection or as a solution *via* gavage to fasted intact male Wistar rats (5 rats/group) or bile duct-cannulated rats (5 rats/group) and as an intravenous bolus injection (5.77 mg/kg equivalent to 4.21 mg/kg of sorafenib) or as a solution in a capsule (5.65 mg/kg equivalent to 4.12 mg/kg sorafenib) to 6 fasted female Beagle dogs (3 dogs/group). After intravenous and oral administration the radioactivity was mainly excreted *via* the biliary/fecal route (90%), urinary excretion was low (<1%). In man, renal excretion of radioactivity was more pronounced than in rat and dog due to species-dependent formation of sorafenib glucuronide, which was excreted into human urine.

- Pharmacokinetic drug interactions

Warfarin, propranolol, nifedipine, furosemide, digitoxin, taxotere, taxol, iressa and cisplatin did not influence the binding extent of sorafinib in any concentration tested (3-15mg/l, 1-5mg/l, 1-5mg/l, 0.5-2.5mg/l, 0.1-0.5mg/l, 3-15mg/l, 2.5-12.5mg/l, 0.5-2.5mg/l, 10-5-mg/l, respectively. Salicylic acid and ibuprofen (200 and 50 mg/l) did not alter fraction unbound (control value 0.275 %) whereas at 1000 and 250 mg/l the fraction unbound increased to 1.50 and 2.70 %, respectively.
The potential of sorafenib to induce human CYP1A2 and 3A4 was investigated in cultured human hepatocytes. Cells were exposed with 0.01 to 50 µg/ml sorafenib for five days in comparison to the prototypic inducers omeprazole (OME, CYP1A2), rifampicin (RIF, CYP3A4), and phenobarbital (PB, CYP3A4). The study revealed no inductive effect of sorafenib on human CYP1A2 and CYP3A4 after repeated exposure up to a concentration of at least 3 µg/ml, whereas OME (100 µM), RIF (50 µM), and PB (2 mM) showed their inducer-specific changes of the CYP isoform activities.
The inhibitory potency of sorafenib towards human cytochrome P-450 isoforms was investigated. Only small inhibitory effects on CYP2C19, 2D6, and 3A4 were observed (Ki = 17 µM, 22 µM, and 29 µM, respectively). Sorafenib inhibited CYP2B6, 2C8, and 2C9 activities (Ki = 5 - 6 µM, 1 - 2 µM, and 7 - 8 µM, respectively). The potency of sorafenib to inhibit single CYP isoforms was according to

the following order: CYP2C8 > CYP2B6, CYP2C9 > CYP2C19, CYP2D6, CYP3A4. CYP inhibition caused by metabolite M-2 was in the same range as for sorafenib itself.
The inhibitory potency of sorafenib towards five human UDP-glucuronosyltransferases and towards acetaminophen glucuronidation, catalyzed by multiple UGTs, was investigated. Propofol was selected as suitable selective substrate for UGT1A9 and its glucuronidation was significantly inhibited by sorafenib (Ki = 2.2 μM). Sorafenib was also a substrate of UGT1A9 (Km = 3 – 8 μM). 3-Glucuronidation of estradiol as well as SN-38 glucuronidation were strongly inhibited (Ki =1.0 μM and 2.7 μM, respectively).
Sorafenib (100 and 200 μM) did not affect biotransformation of [14C] 5-fluorouracil *in vitro*, whereas uracil (100 μM, positive control) as a substrate of dihydropyrimidine dehydrogenase inhibited 5-fluorouracil metabolism to one third of control activity.

- Other pharmacokinetic studies

The metabolic pattern in plasma of male Wistar rats was investigated following oral administration of 5 mg/kg [14C] M2, the major human circulating metabolite identified. There was a time-dependent decrease of [14C] M2 from 96 % (after 30 minutes) to 6 % of the radioactivity present in plasma, 48 hours following administration. After 7 hours M2 was still the major component. In terms of AUC, M2 represented the majority of the radioactivity present in plasma (57.8 %). M2 moderately inhibited CYP2B6, 2C9, 2C19, 2D6, and 3A4 and exhibited a more pronounced inhibitory effect on CYP2C8.

Toxicology

- Single dose toxicity

The toxicity of single doses of sorafenib has been investigated *via* the oral route in mice, rats and dogs. The highest single oral sorafenib dose of 1460 mg/kg was tolerated in mice and rats without any sign of toxicity. In Beagle dogs, vomiting was observed after a single oral dose of 120 mg/kg solution, and 1000 mg/kg powder (1370 mg/kg of the tosylate salt) After administration of two times 24 hours i.p doses of 125-500 mg/kg of sorafenib in mice, apathy, roughened fur, hard abdomen, spasm, periodically stretching of body and difficulty in breathing were observed but mortality was not induced. At 500 mg/kgone male died. At the 1000 mg/kg dose, all males and one female died.

- Repeat dose toxicity (with toxicokinetics)

The long term toxicity of sorafenib was tested in mice (3 months), rats (up to 6-month), Beagle dogs (up to 12 months).
A group of 10 male and 10 female Wistar rats were treated orally for 4 weeks at 0 -125 mg/kg dose of sorafenib. Mortalities prior to the end of 4 weeks treatment included 3 males and 9 females at 25 mg/kg, 3 males and 1 female at 125 mg/kg. Dose-dependent clinical signs of toxicity were noted at 5 mg/kg and above. In the clinico-chemical investigations, increases were seen in AST, ALT (beginning at 1 mg/kg), GLDH and LDH (at 25 and 125 mg/kg), cholesterol and bilirubin (beginning at 5 mg/kg). An increase was seen in alkaline phosphatase (ALP) at 5 mg/kg with decreases at 25 and 125 mg/kg. In urine, increases were seen in protein, urine creatinine (in females only), NAG, and LDH, particularly at 25 and 125 mg/kg. Histopathological evaluation revealed treatment-related findings in the majority of animals treated at 25 or 125 mg/kg. Overall, the changes were classified as degenerative in the adrenal glands, liver, stomach, duodenum, pancreas, kidneys, heart, and ovaries. Regenerative changes were observed in the liver (bile duct proliferation), pancreas, duodenum and kidneys. Necrosis was observed in the spleen, lymph nodes, and thymus. Effects in male reproductive organs included retardation in testes, epididymides, prostate and seminal vesicles. Most of the findings could be shown to be reversible. However, bile duct proliferation, liver fibrosis, effects on lymphoreticular system were still visible at the end of the 1-month recovery period. A NOAEL was not established.
In a 6 month toxicity study,20 male and 20 female Wistar rats were treated daily orally by gavage at 0 -2.5 mg/kg dose of sorafenib. The lowest dose causing significant toxicity (LOAEL) was 1 mg/kg/day. A NOAEL was not established for females.

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In a 4-week study in dogs with initial twice-daily administration of 10, 30, or 60 mg/kg, both 30 mg/kg bid and 60 mg/kg bid of sorafenib induced emesis, bloody diarrhoea and reduced body weight gain > Dosing was therefore reduced to once daily after one week of treatment.
After the administration of 30 mg/kg of sorafenib, once-daily for 3 or 12 months in dogs, effects on the GI tract (bloody diarrhoea) and on the skin (hair loss, inflammation) were observed. At histopathology, degenerative and regenerative processes were seen dose-dependently in multiple tissues including kidneys, lymphoreticular / hematopoetic system, GI tract, adrenals, teeth and bone. Marked morphological changes were observed in the liver and skin. The morphological no-effect-level after 3 or 12 months treatment was below 10 mg/kg/day.

- Genotoxicity

The genotoxicity of sorafenib tosylate was studied with respect to gene mutations in bacteria, chromosomal aberrations *in vitro* in Chinese hamster V79 cells, and *in vivo* in the mouse micronucleus test in bone marrow. Sorafinib was investigated using the Salmonella/microsome plate incorporation test for point mutagenic effects in doses of up to 5000 µg per plate on five Salmonella *typhimurium* LT2 mutants. Doses up to 8µg per plate did not cause any bacteriotoxic effects. Total bacteria counts remained unchanged and no inhibition of growth was observed. At higher doses the substance had a strong, strain-specific bacteriotoxic effect. Evidence of mutagenic activity of sorafenib was not seen. No biologically relevant increase in the mutant count was observed. The cytogenetics *in vitro* test for clastogenicity using Chinese hamster V79 cells was negative without metabolic activation, but was positive for clastogenicity in the cytotoxic range of doses (cytotoxicity starting at 40 µg/ml) following addition of a liver microsome preparation (S9-mix). The Micronucleus test for clastogenicity in NMRI mice with intraperitoneal sorafenib tosylate doses of 0, 125, 250, or 500 mg/kg (sorafenib dose up to 365 mg/kg) was negative.

- Carcinogenicity

Carcinogenicity studies were not conducted with sorafenib.

- Reproductive and developmental toxicity

Developmental toxicity studies were performed in rats and rabbits. Twenty-two inseminated female Wistar rats were treated orally by gavage with sorafenib tosylate. The rats were treated from day 6 to 17 *post conceptionem* with sorafenib doses of 0 to 2.5 mg/kg/day. Treatment-related effects were observed at 2.5 mg/kg and included impaired gestation rate (one total late resorption), increased post-implantation loss (late resorptions) and consequently decreased mean litter size, increased incidence of necrotic placental borders and pale placentas, decreased placental and fetal weights, retarded fetal skeletal ossification in relation to reduced fetal weights and increased incidence of external and visceral deviations (pale appearance, missing innominate artery) and skeletal variations (supernumerary 14th ribs). Incidence of generally common fetal malformations of different types was as well increased at 2.5 mg/kg. The NOAELs determined for systemic maternal toxicity and intrauterine development were 1 mg/kg/day and 0.2 mg/kg/day, respectively.
Twenty female Himalayan rabbits were treated daily by oral administration (gavage) with sorafenib tosylate from days 6 to 20 *post conceptionem* with 0 to 3 mg/kg dose of sorafenib. Sorafenib induced teratogenic effects at 3 mg/kg/day ($AUC_{0\text{-}24h}$ 12 mg.h/l; 0.1 times the expected clinical exposure). Increased incidence of fetal malformations mainly malformations of kidneys, vertebrae, and ribs was seen at 3 mg/kg/day. A treatment-related effect on external and visceral deviations was not evident at doses up to and including the highest tested dose (3 mg/kg/day). Skeletal development (retardations/variations) revealed an increased incidence of fused sternebrae and retarded ossification of cervical vertebral bodies and frontal bones at 3 mg/kg/day. Fetal sex distribution was shifted to 40% males at 3 mg/kg/day. At 3 mg/kg/day, decreased maternal weights, decreased gestation rate due to the abortion of one female, and by three females, which showed total resorptions, incidences of placental findings (partly necrotic placentas), increased postimplantation loss in females with viable fetuses, mainly caused by late resorptions and decreased mean number of fetuses were observed. Increased

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incidence of females with cold ears (transient occurrence) increasing with dose (NOAEL was < 0.3 mg/kg/day in maternal and NOAEL was 1 mg/kg in pups).
In the 4-,13- and 26- week study in rats, treatment-related effects at a dose of 25 mg/kg/day of sorafenib were observed (in male reproductive organs included retardation in testes, epididymides, prostate and seminal vesicles; in females there were retarded ovaries and central necrosis of corpora lutea).
Dogs showed tubular degeneration in a 12-month study at 30 mg/kg/day, and oligospermia in the epididymides was found at 60 mg/kg/day.

- Local tolerance

In rabbits, sorafenib was not irritant to the skin or to the eyes and there were no systemic intolerance reactions ([29, 30])

- Other toxicity studies

Immunotoxicity
No specific studies to investigate immunotoxicity were performed.

Metabolites
M-2 has been toxicologically characterised with respect to genotoxicity (*in vitro* bacterial mutation) and repeat dose toxicity (1-month oral rat study). M-2 did not induce genotoxic effects *in vitro* in the Ames test. In the repeat dose toxicity study survival as well as the appearance or behavior of the rats were not affected by treatment with M2. At 5 and 25 mg/kg, the animals exhibited slight body weight retardation. Results from urinalysis were unremarkable. Hematology revealed slightly elevated numbers of erythrocytes, hemoglobin and hematocrit at 5 and 25 mg/kg, in addition slightly reduced platelet counts in 25 mg/kg rats. Blood clinical chemistry revealed a tendency to increased activities of AST and ALT in rats receiving 5 or 25 mg/kg, plasma concentrations of triglycerides were slightly reduced after 25 mg/kg. At histopathology, the only remarkable finding was a treatment-related dentin alteration and increased numbers of adipocytes in the bone marrow of 5 and 25 mg/kg animals. There was no morphological correlate for the elevated serum markers for liver toxicity and decreased liver weights observed at necropsy. The NOAEL was 1 mg/kg/day.

Studies on impurities
Two impurities have been toxicologically characterised in genotoxicity trial (*in vitro* bacterial mutation).
An Ames test and a repeat-dose (4-week) toxicity study in rats were performed with PAPE-urea. There was no indication for a genotoxic potential of PAPE-urea. In the 4-week rat study with experimental conditions the highest dose tested, 1000 mg/kg/day, was tolerated without any signs of systemic toxicity.
For the second impurity (PAPE) an Ames test was positive after metabolic activation (S9-mix), with a lowest effect-dose of 624 µg/plate, but negative without metabolic activation. One batch, which contained 0.34% PAPE was tested in the Ames test, the chromosomal aberrations test and in the *in vivo* micronucleus test, no genotoxic effect was seen in either the Ames test or the micronucleus test. However, genotoxic effects were induced in the chromosomal aberration test.

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Ecotoxicity/environmental risk assessment

The calculated $PEC_{SURFACEWATER}$ was below the action limit of 0.01µg/l, taking individual market penetration factors into consideration.

Discussion on the non-clinical aspects

Pharmacology

Sorafenib was highly efficacious *in vivo* in renal tumour xenograft models (RENCA model). Anti-tumour efficacy was also demonstrated *in vivo* in a number of different non-renal tumour xenograft models by affecting the RAS/RAF/MEK pathway. This included xenograft models of human colon, lung, breast, melanoma, leukaemia, pancreatic, and ovarian cancer. The efficacy of sorafenib against this tumour models suggested that a RAF kinase inhibitor may have utility not only in human tumours containing ras and/or b-raf mutations, but also in tumours that overexpress other growth factor receptors that signal through the same pathway. Furthermore, sorafenib was very effective against the MV4-11 AML model that expresses an activating Flt3 mutation. In cellular assays *in vitro*, sorafenib inhibited the RAF/MEK/ERK pathway in breast, pancreatic, melanoma, and colon tumour lines as evidenced by reduction of phospho-ERK levels including cell lines expressing either wild-type or mutant k-RAS or BRAF. However, inhibition of the RAF/MEK/ERK pathway was not observed in the non-small cell lung cancer (NSCLC) lines A549 and H460, at concentrations up to 20 µM sorafenib. The mechanism underlying the lack of inhibition of ERK phosphorylation in these cell lines has not been elucidated.
No direct comparison was made non-clinically between a tumour model that expresses a wild type VHL and a VHL mutant subline of the same model. Sorafenib was active against the 786-0 human renal tumour model that has a VHL deletion and was less active against the CAKI-1 human renal tumour model that expresses wild type VHL. However, since these two tumour lines were derived independently from separate patients, it could not be concluded that the difference in VHL status was solely responsible for the different sensitivity to sorafenib. Although this data could help to predict the sensitivity of a human tumour to sorafenib therapy, limited data did not support patient selection for sorafenib treatment based on this biomarker (see clinical pharmacology section).

Pharmacodynamic drug interactions were studied in several non-clinical tumour xenograft models. The results suggested that sorafenib can be combined with paclitaxel, irinotecan, gemcitabine, gefitinib and cisplatin with no significant increase in the toxicity and without diminishing their anti-tumour efficacy. However, the combination of sorafenib and doxorubicin required reduction of the dose level of both agents to attain acceptable tolerance and efficacy (see clinical pharmacokinetc section).

The metabolites M-2, M-4 and M-5 inhibited several receptor tyrosine kinases including VEGFR-2, PDGFR-β, and Flt-3, showing a similar *in vitro* pharmacological activity as sorafenib, but they were present at much lower plasma levels. Thus, the metabolites did not much contribute to the overall activity. The most predominant human metabolite, M-2, was also evaluated *in vivo* for anti-tumour efficacy against the MDA-MB-231 xenograft model and was less active than the parent compound. However, the degree to which M-2 contributed to the anti-tumour efficacy of sorafenib could not be determined as M-2 was partially converted to sorafenib *in vivo*.

Pharmakokinetics

Sorafenib was almost completely absorbed in mice and rats and moderately absorbed in dogs. Sorafenib and/or its metabolites were widely distributed, crossed the blood-brain barrier and penetrated the placental barrier. In animals, sorafenib and/or its metabolites were excreted into milk. It is not known whether sorafenib is excreted in human milk. Because sorafenib could harm infant growth and development, breast-feeding is contraindicated during sorafenib treatment (see SPC sections 4.3, 4.6 and 5.3).
In human, sorafenib was subject to two important biotransformation pathways. Formation of M-2 was catalyzed by CYP3A4 and formation of the drug glucuronide M-7 was mediated by UGT1A9. Additionally, human kidney was also capable of forming glucuronide M-7. *In vitro* incubations of

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[^{14}C]sorafenib tosylate with liver microsomes of human and animal species revealed two phase I reactions to be prominent: hydroxylation of the N-methyl group yielding metabolite M-3 and N-oxidation at the pyridine moiety yielding metabolite M-2. Based on comparison of metabolite profiles, mouse and rat was considered roughly similar to human. M-2, however, was only formed in smaller amounts in dogs and rabbits. Rhesus monkey was regarded as most similar to human.
Sorafenib did not induce human CYP1A2 and CYP3A4 in cultured human hepatocytes. Sorafenib was capable of inhibiting CYP2C8, CYP2B6 and CYP2C9 activities in human liver microsomes whereas only small inhibitory effects on CYP2C19, CYP2D6, and CYP3A4 were observed. Glucuronidation of propofol (UGT1A9) was significantly inhibited. 3-Glucuronidation of estradiol (UGT1A1) as well as SN-38 glucuronidation (UGT1A1) were strongly inhibited. Sorafenib did not inhibit dihydropyrimidine dehydrogenase *in vitro*. Hence, clinical drug interactions might be expected due to inhibition specifically of the CYP2C8, CYP2B6, CYP2C9, UGT1A9 and UGT1A1 enzymes (see SPC, section 4.4 and 4.5, see also clinical pharmacokinetic section).

Toxicology

The toxicology of sorafenib was investigated in accordance with the European guidelines [31],[32]. Sorafenib was of low acute toxicity. Single-dose studies with intravenous administration were not performed due to the very low solubility of sorafenib in suitable vehicles. When comparing non-lethal doses, the multiple to human maximum dose (13 mg/kg) was approximately 100 in the mouse and rat, and 75 in the dog. In repeat-dose toxicity studies, the MTD was 100 mg/kg/day in mice (3-months), 5 mg/kg/day in rats (3-months) and >60 mg/kg/day in dogs (12-months). The main target organs of toxicity with possible impact on the human risk assessment were: liver, kidneys, gastrointestinal-tract, cardio-vascular system, lymphoreticular/hematopoietic system, adrenals, reproductive organs, teeth, bone, and skin. Some of the morphological lesions were fully reversible or showed at least a tendency towards recovery. However, bile duct proliferation, liver fibrosis, effects on lymphoreticular system were still visible at the end of the 1-month recovery period. Effects on the liver were observed in mice, rats and dogs after repeated oral administration. Increased levels of ALT, AST, GLDH and ALP in serum were accompanied by histopathological changes and also mostly by decreased liver weights. The estimated exposure multiple towards the estimated clinical exposure was 1-3, 0.7 and <0.2 in mice, rats and dogs, respectively. An anti-diuretic effect and histopathologically nephropathy including tubular dilation, hyaline casts and basophilic tubules were observed in different animal studies. The exposure multiple towards the estimated clinical exposure was 2-4, 0.1 and <0.2 in mice, rats and dogs, respectively.
Effects on peripheral white and red blood cell serum parameters or on blood coagulation parameters were observed at relatively low dose levels in the repeat dose studies. The observations were often accompanied by changes in the blood-forming elements (bone marrow, spleen) and immune organs (thymus, spleen) but then mostly at a slightly higher dose to where haematological changes were noted. The exposure multiple towards the estimated clinical exposure was 0.5-3, <0.7 and <0.2 in mice, rats and dogs, respectively. In young and growing dogs after repeated dosing, irregular thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate, and alterations of the dentin composition in the teeth were observed. In aged adult dogs, no treatment related morphological changes in the femoral bone or in the teeth were observed. In rats and mice after repeated dosing, marked effects on the teeth including altered dentin composition were observed. The extrapolation of these findings to the human is difficult as in contrast to humans, the teeth of the rodent species used (in particular the incisors) are continuously growing through the life of the animal. The LOAEL for bone was, 5 mg/kg/day (rat, 6-month) and 10 mg/kg/day (dog). The exposure multiple towards the estimated clinical exposure was 0.7 and <0.2 in rats and dogs, respectively. The LOAEL for teeth was 100 mg/kg/day (mice), 0.1 mg/kg/day (female rat, 6-month) and 30 mg/kg/day (dog). The exposure multiple towards the estimated clinical exposure was 1-3, 0.01 and <0.5 in mice, rats and dogs, respectively. Overall, a potential risk of toxicity on bone and teeth of children or adolescents cannot be excluded (see SPC section 5.3).
The standard program of genotoxicity studies was conducted and positive results were obtained as an increase in structural chromosomal aberrations in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity in the presence of metabolic activation was seen. Sorafenib was not genotoxic in the Ames test or in the *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (< 0.15%), was positive for

mutagenesis in the Ames test. Furthermore, the sorafenib batch tested in the standard genotoxicity program included 0.34% PAPE. Studies to evaluate the carcinogenic potential of sorafenib have not been performed. The omission of carcinogenicity studies is acceptable for this type of compound [5].
No specific studies have been conducted in animals to evaluate the effect of sorafenib on fertility. Repeat-dose studies in animals have shown changes in male and female reproductive organs at exposures below the anticipated clinical exposure (based on AUC). Sorafenib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below the clinical exposure. Therefore, it is recommended that sorafenib is not used during pregnancy unless clearly necessary, after careful considerations of the needs of the mother and the risk to the foetus. Women of childbearing potential must use effective contraception during treatment (see SPC sections 4.6 and 5.3).
Sorafenib and its metabolite M-2 had a similar toxicological profile. The specification limit of 0.15% for two impurities was considered toxicologically qualified and justified in view of its use in patients with advanced renal cancer. A third impurity was considered toxicologically qualified up to 0.74%. Sorafenib was considered unlikely to pose a risk to the environment [33] .

1.4 Clinical aspects

Introduction

The clinical programme of sorafenib comprised seven dose-finding and PK phase I studies involving patients with advanced solid tumours. Patients from these studies were allowed to continue treatment with sorafenib in an extension phase II protocol (study 10922). The phase II program explored signals for efficacy in several tumour types (study 100391 in advanced, refractory colorectal cancer and renal cell carcinoma, and study 10874 in hepatocellular carcinoma). In addition, four studies explored the combination of sorafenib with other antineoplastic agents [oxaliplatin (study 10954), doxorubicin (study 10916), gemcitabine (study 100374), irinotecan (study 10981)]. A phase III pivotal study (study 11213) compared sorafenib 400 mg twice daily with placebo in patients with advanced RCC. The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Sorafenib treatment must be supervised by a physician experienced in the use of anticancer therapies. The recommended dose in adults is 400 mg (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg). It is recommended that sorafenib is administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water. The treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of sorafenib therapy. When dose reduction is necessary, the sorafenib dose should be reduced to two tablets of 200 mg once daily (see section 4.2 and 4.4).

Pharmacokinetics

Pharmacokinetic (PK) plasma samples from clinical studies were analysed for sorafenib using validated HPLC assays with mass-spectrometric detection. The lower limit of quantitation in plasma was 1-10 µg/l for sorafenib (varied by study), 25 µg/l for M1 and 10 µg/l for metabolites M2, M3, M4 and M5. The lower limit of quantitation in urine was approximately 10 µg/l for sorafenib and metabolite M2. Metabolites M7 and M8, glucuronides of parent drug and metabolite M2, respectively, were measured indirectly as sorafenib and M2 after hydrolyzing the corresponding glucuronide. The lower limit of quantitation for both analytes was approximately 14 µg/l based on the conversion factor. Upper calibration range was approximately 10,000 µg/l for sorafenib and metabolite M2 and approximately 14,000 for metabolites M7 and M8. Precision for all analytes for all methods was within 15%, and accuracy was within 85 - 115%. Stability of all analytes was determined under sample handling conditions, freeze-thaw cycles and for the duration the samples from clinical studies were stored prior to analysis. All analytes were stable under those conditions. Cross-validation for

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different analytical sites was performed. Pharmacokinetic parameters were calculated using non-compartmental methods.

- Absorption

In healthy volunteers, sorafenib taken with a moderate-fat meal was rapidly absorbed with a median T_{max} ranging from 4 to 8 hours. In patients, the median T_{max} was approximately 3 hours (range 0-24 hours). Secondary absorption peaks were observed at 8-12 and 24 hours postdose, indicating enterohepatic re-circulation.
Permeability evaluations in Caco-2 cells indicated that sorafenib is a highly permeable compound based on comparison with 22 reference compounds. The efflux ratio of sorafenib for transport from basolateral to apical side to transport from the apical to basolateral side of Caco-2 cells was 4.7 and 2.5 at 0.1 and 1 µM sorafenib, respectively, indicating significant but saturable efflux. However, the efflux ratios for known substrates of efflux pumps such as vinblastine (29.6) and sulphasalzine (42.3) were higher, indicating that sorafenib is a weak substrate for an efflux pump. Sorafenib efflux was also evaluated in monolayers of P-gp-expressing L-MDR1 cells in the presence and absence of ivermectin, a potent P-gp inhibitor. In this study the efflux ratio was 6.78 and 4.25 at 0.1 and 1 µM sorafenib, respectively. The sorafenib efflux was inhibited by ivermectin. The efflux ratios for sorafenib in this experiment were in the same range as those reported in the literature for prazosin (4.6) and vincristine (6.3). Efflux ratio reported for paclitaxel in P-gp over-expressing cells is >108. The efflux observed for sorafenib was low to moderate.

Bioavailability

The absolute bioavailability of sorafenib has not been determined as no intravenous formulation has been developed. The pharmacokinetic parameters of sorafenib following the administration of a single oral doses of sorafenib given as liquid formulation (polysorbate 80-based oral solution) or as 50 mg tablets to patients are provided in the table below.

Table 2: PK parameters of sorafenib following single oral dose given as liquid formulation or as 50 mg tablets [geometric means / (%CV)] (n=3 / cohort)

Parameter	Unit	Liquid formulation		50 mg tablet	
Dose		**100 mg**	**200 mg**	**100 mg**	**400 mg**
AUC	mg∗h/l	64.6 / 63%	59.7 / 51%	24.5 / 52%	58.3 / 22%[b]
C_{max}	mg /l	2.10 / 22%	2.10 / 21%	0.75 / 34%	3.53 / 31%
t_{max}[a]	h	2.5 (1.0-6.0)	3.0 (2.5-3.0)	8.0 (8.0-12.0)	3.1(3.0-3.1)
$t_{½}$	h	34.9 / 51%	32.1 / 26%	38.0 / 10%	

[a] median (range); [b] AUC_{0-tn}

Bioequivalence

In one study (n=26-34), similar exposures were obtained with a single 400 mg dose given either as 50 mg tablets or as 200 mg tablets.

Influence of food

The pharmacokinetics of sorafenib after a single 400 mg (given as 200 mg tablets) dose were evaluated in 15 healthy volunteers (study 100484) following administration of a high-fat breakfast, a moderate-fat breakfast and administration in the fasted state. Sorafenib bioavailability from tablets following administration of a moderate-fat breakfast was almost similar to that when administered in the fasted state, although there was a trend towards increased AUC (14%). However, when given with a high-fat breakfast, sorafenib absorption was reduced by approximately 29% compared to administration in the fasted state. Study 100545 confirmed that concomitant administration of a moderate-fat meal with 400 mg sorafenib (given as 50 mg tablets) in 29 healthy volunteers had no influence on AUC of sorafenib compared to fasted dosing.
The solubility of sorafenib tosylate ranges from 0.034 mg/100ml at pH 1.0, to 0.013 mg/100ml at pH 4.5. The influence of intra-gastric pH on sorafenib pharmacokinetics is described in the PK interaction studies (antiacids) section (see also discussion on clinical PK).

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- Distribution

As there was no study with intravenous administration of sorafenib, the volume of distribution was determined. Apparent volume (V/F) was not reported.
Sorafenib and its main metabolite in plasma (M2) were to 99.5% bound to plasma proteins. Protein binding was linear across concentrations. Sorafenib and M2 were primarily bound to serum albumin and to a lesser extent to α-globulins, β-globulins and LDL but not to γ-globulins and α_1-acid glycoprotein. Sorafenib was distributed between red blood cells and plasma with a plasma to blood ratio of 1.33. In man, total plasma radioactivity and sorafenib were subject to enterohepatic circulation as indicated by several secondary maxima of the plasma concentration time curves and was explained by two different processes: i) glucuronidation of the drug, biliary excretion of the glucuronidated metabolite M7 into the gut, cleavage of the glucuronide and reabsorption of sorafenib, ii) oxidation of the drug to metabolite M2, biliary excretion of M2 into the gut, reduction by colonic bacteria to sorafenib and reabsorption.

- Metabolism

The biotransformation of sorafenib *in vitro* was investigated using liver microsomes of several animal species and humans, microsomes containing heterologously expressed human cytochromes or glucuronosyl transferases and rat and human hepatocytes (see non-clinical section). Table 3 provides a summary of the identified metabolites formed in human, *in vivo* and/or *in vitro,* and their occurrence in plasma, faeces and urine over 192 hours sampling after a single dose in the mass-balance study.

Table 3: The human metabolites of sorafenib and their occurrence after a single dose

Substance		**Plasma (% of total radioactivity)**	**Faeces (% of dose)**	**Urine (% of dose)**
Sorafenib		73%	50.7%	nd
M1	Combination of N-oxidation and N-methylhydroxylation	nd	nd	nd
M2	N-oxidation	16.7%	nd	nd
M3	N-methylhydroxylation	trace amounts	0.4%	nd
M4	demethylation	1%	1.2%	nd
M5	oxidative metabolite	nd	nd	nd
M6	carboxylic acid	trace amounts	19.1%	nd
M7	glucuronide of sorafenib	0.5%	nd	14.8%
M8	glucuronide of M2	nd	nd	2.7%

nd = not detected

At 400 mg b.i.d. multiple dosing, metabolites M2 and M4 accumulate to a similar extent as sorafenib. At steady state, metabolite M2 exposure was16% (sum of parent and measured metabolites) and M4 exposure was 8% of the total exposure. Metabolites M2 and M4 reached a steady state after 7 days of dosing. M5 was 6% of the total exposure at steady state. M5 reached a steady state after 14 days of dosing. The major metabolite M2 was eliminated *via* further metabolism to M1, glucuronidation to M8 and possibly biliary excretion.

- Elimination

The mean terminal half-life determined for sorafenib across studies varied between 25-48 hours.
The disposition and excretion of sorafenib and its metabolites was evaluated in a clinical mass-balance study with a single oral administration of 100 mg ^{14}C-sorafenib as oral solution to four healthy male volunteers. A total of 96% of the dose was recovered in excreta within 14 days, and 77% of the radioactivity was recovered in faeces. Unchanged sorafenib was the major constituent in faecal extracts (51% of the dose). About 10% of the dose (5-8% of the dose as unchanged drug) was recovered in the first faecal sample (0-48hr), while the largest fractions of the dose (25-38% of the dose as total radioactivity or 19-25% as unchanged drug) was found in the second (48-72 hr) or third (72-96%) samples. The major metabolite in faeces was the carboxylic acid M6 (9.1 % of the dose).

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M3 and M4 were minor metabolites (0.4% and 1.2% of the dose, respectively). M2 was not found in faeces, likely due to its instability towards intestinal bacteria.
Approximately 19% of the dose was recovered in urine as glucuronidated metabolites. No unchanged sorafenib was found in urine, but two metabolites, M7 and M8 could be detected and identified as glucuronide of sorafenib and glucuronide of the predominant plasma metabolite, M2, respectively. M7 accounted for 78.6 % and M8 for 14.1 % of the radioactivity in urine, respectively (14.8 % and 2.7 % of the dose, respectively).

- Dose proportionality and time dependencies

With the oral solution, the exposure did not increase linearly at doses of 100 mg and higher in a multiple-dose study in patients. However, with b.i.d. dosing, there was a dose-dependent increase in AUC with increasing dose up to 400 mg b.i.d. administered as tablets, although the variability was high within and between studies. At higher doses, exposure increased less than proportionally with dose: Mean $AUC_{(0-12),ss}$ values at the 600 mg b.i.d. dose level were slightly greater than those at 400 mg b.i.d. and mean $AUC_{(0-12),ss}$ at the 800 mg dose level was not greater than that at 600 mg b.i.d (see table 4).

Sorafenib exposures reach steady state after 7 days of dosing. With 400 mg b.i.d. dosing, there was on average a 4-fold and 4.7-fold accumulation at steady state in Cmax,ss and AUC(0-12),ss values, respectively.

Table 4: Mean plasma pharmacokinetic parameters following 28 days of dosing in patients (study 100277)

Dose		**AUC_{0-24} -(mg*h/l)**	**AUC_{0-12} (mg*h/l)**	**C_{max} (mg/l)**		**$t_{1/2}$ (h)**
		Day 1	**Day 28**	**Day1**	**Day 28**	**Day 28**
100 mg once daily	N	3	4	4	4	2
	mean (CV%)	8.75 (35.1)	15.06 (64.6)	0.81 (37.6)	0.85 (62.0)	23.8 (1.7)
100 mg bid	N	2	3	3	3	3
	mean (CV%)	6.13 (74.0)	45.98 (36.7)	0.81 (61.3)	5.4838.9)	35.5 (74.6)
200 mg bid	N	4	5	6	5	4
	mean (CV%)	10.88 (38.4)	34.72 (43.8)	1.34 (33.8)	3.95 (52.3)	31.8 (10.1)
400 mg bid	N	4	3	4	3	3
	mean (CV%)	**21.81** (58.8)	**47.78** (24.0)	**2.87** (68.4)	**5.37** (41.0)	**27.4** (24.1)
600 mg bid	N	3	5	7	5	4
	mean (CV%)	10.06 (96.7)	38.09 (36.8)	2.00 (71.5)	4.71 (28.5)	26.3 (27.1)

Sorafenib exhibits relatively high inter- and intra-patient pharmacokinetic variability in exposure with coefficients of variation around 61%-65% and 44%-47%, respectively.

- Special populations

Impaired renal function: A retrospective evaluation across studies was made to evaluate the relationship between calculated creatinine clearance and steady-state exposure to sorafenib. Pharmacokinetic data were available from 4 patients with a calculated creatinine clearance in the range of 30-50 ml/min, 24 patients in the range of 50-80 ml/min and 71 patients in the range of >80 ml/min. Data were only presented for patients receiving the 400 mg dose b.i.d (phase I studies 10164, 100277, 100283, 100342), which did not include patients with creatinine clearance < 60 ml/min. Steady state exposure to sorafenib was similar in patients with mild or moderate renal impairment compared to the exposures in patients with normal renal function.

Impaired hepatic function: Pharmacokinetic data was obtained in a phase II study (10874) in patients with hepatocellular carcinoma [Child-Pugh A (n=14) or B (n=8)] receiving sorafenib 400 mg bid. Patients with Child Pugh B, compared with patients with Child Pugh A, had numerically higher AUC_{0-8hr} [geometric mean (%CV) = 30.3 (82.1) *vs* 25.4 (38.4)] and C_{max} [geometric mean (%CV) = 5.97 (73.8) *vs* 4.92 (38.7)] values for sorafenib (differences not statistically significant). Exposure to

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metabolite M5 was slightly lower in Child-Pugh B patients, while there were no differences between the two groups for M2 and M4.

Gender: A retrospective evaluation across studies (10164, 100277, 100283 and 100342) did not indicate a relationship between gender and steady state plasma sorafenib $AUC_{(0-12),ss}$ values following administration of 400 mg bid of sorafenib. No evaluation of the relationship between CL/F and gender was presented.

Race: Steady state plasma sorafenib AUC(0-12),ss and Cmax,ss values in Oriental (Japanese) patients (studies 10658 and 11497) were compared with those in Caucasian patients (studies 10164, 100277, 100283 and 100342) across studies. While the mean sorafenib $C_{max,ss}$ [geometric mean (%CV) = 4.91 (76) *vs* 8.3 (57.4)] and $AUC_{(0-12),ss}$ [geometric mean (%CV) = 36.7 (73) *vs* 67.3 (56.8)] values were lower in Japanese patients (n=6) compared to Caucasian patients (n=27) receiving sorafenib 400mg b.i.d. and for other dosages (data not shown), there was a significant overlap in the range of exposures observed in these two groups. Sorafenib had high inter-patient pharmacokinetic variability in both patient groups.

Weight: A retrospective evaluation across studies (10164, 100277, 100283 and 100342) did not indicate a relationship between body weight and steady state sorafenib $AUC_{(0-12),ss}$ values following administration of 400 mg bid of sorafenib.

Elderly: A retrospective evaluation across studies (10164, 100277, 100283 and 100342) did not indicate a relationship between age and steady-state exposure to sorafenib. No evaluation of the relationship between CL/F and age was made. There were only 3 patients above 65 years in the presented evaluation of the 400 mg dose.

Children: There were no PK data available in children.

- Pharmacokinetic interaction studies

Inhibition of cytochrome P450
The potential of sorafenib to inhibit cytochrome P450-mediated metabolism *in vitro* was investigated using recombinant enzymes as well as human liver microsomes. Table 5 summarises the results of these studies.

Table 5: Inhibitory effects of sorafenib on formation of metabolites from standard probes mediated by CYP isoforms

CYP isoform	Substrate	Enzyme source	Ki [µM]
1A2	Phenacetin	Recombinant enzyme	232
	Phenacetin	Human liver microsomes	n.i.
2A6	Coumarin	Recombinant enzyme	n.i.
2B6	7-Ethoxytrifluoromethylcoumarin	Recombinant enzyme	6.2
	Bupropion	Human liver microsomes	5.1
2C8	Taxol	Recombinant enzyme	2.4
	Amodiaquine	Recombinant enzyme	0.7
2C9	Diclofenac	Recombinant enzyme	7.3
	Tolbutamide	Recombinant enzyme	7.7
2C19	S-Mephenytoin	Recombinant enzyme	17
2D6	Bufuralol	Recombinant enzyme	4.0
	Dextromethorphan	Human liver microsomes	22.2
2E1	Chloroxazone	Recombinant enzyme	n.i.
3A4	Testosterone	Human liver microsomes	26.3
	Midazolam	Human liver microsomes	28.9

n.i = no inhibition

In an *in vitro* study with pre-incubation with sorafenib in the presence and absence of NADPH, the inhibition of CYP2C9, CYP2D6 and CYP3A5 was neither time- nor NADPH dependent. The inhibitory potency of M2, towards 8 human CYP isoforms was investigated. M2 moderately inhibited CYP2B6, 2C9, 2C19, 2D6, and 3A4 and exhibited a more pronounced inhibitory effect on CYP2C8.

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Inhibition of UDP-glucuronosyltransferases
The inhibitory potency of sorafenib towards five human UDP-glucuronosyltransferases (UGTs) and towards acetaminophen glucuronidation, was investigated. The glucuronidation of propofol, a substrate for UGT1A9, was inhibited by sorafenib (Ki = 2.2 μM). Sorafenib also inhibited UGT1A1 as shown by an inhibition of the glucuronidation of estradiol as well as SN-38 (active metabolite of irinotecan) with Ki =1.0 μM and 2.7 μM, respectively. Following repeated administration of 400 mg b.i.d. of sorafenib to patients, plasma levels (C_{max}) were above Ki values towards UGT1A1 and 1A9. Sorafenib did not significantly inhibit UGT1A4, UGT1A6 and UGT2B7 as indicated by IC50 values of 61 μM (UGT1A4) or > 100 μM sorafenib. Acetaminophen glucuronidation was not significantly inhibited. Genetic polymorphisms of UGT1A9 have been identified. Two alleles UGT1A9*3 [34-37] and UGT1A9*5 [38] have been associated with decreased glucuronidation activity. However, functional consequences of the UGT1A9 polymorphism are not yet well understood.

Inhbition of dihydropyrimidine dehydrogenase
Hepatic dihydropyrimidine dehydrogenase has been recognised as the relevant enzyme determining plasma and tissue concentrations of 5-fluorouracil in man. The inhibitory potency of sorafenib towards this enzyme was investigated in human liver cytosolic fractions. Sorafenib (100 and 200 μM) did not affect biotransformation of [^{14}C] 5-fluorouracil *in vitro*.

Inhibition of P-gp
In L-MDR1 cells, sorafenib concentration-dependently inhibited the active efflux of loperamide and dipyridamole. The IC_{50} for the inhibition of loperamide and dipyridamole efflux amounted to 0.84 μM and 1.24 μM, respectively. These IC_{50} values were significantly lower than the plasma concentrations of sorafenib observed during clinical studies.

Induction of cytochrome P450
The potential of sorafenib (0.01 to 50 μg/ml) to induce human CYP1A2 and 3A4 was investigated in cultured human hepatocytes of two different donors. Omeprazole, rifampicin and phenobarbital were used as positive controls. No inductive effect of sorafenib on human CYP1A2 and CYP3A4 after repeated exposure up to a concentration of 3 μg/ml was observed.

Ketokonazol
An interaction study was performed with 50 mg sorafenib and 400 mg ketokonazole (CYP3A4 inhibitor) in a one-way cross-over study in 16 healthy male volunteers. Ketoconazole caused no increase in sorafenib AUC [ratios of LS means: 0.89, 90% CI (0.69, 1.14)] and Cmax [ratios of LS means: 0.74, 90% CI (0.56, 0.97)] values and no change in its half-life [ratios of LS means: 1.01, 90% CI (0.80, 1.29)] in the absence and presence of ketoconazole administration. These data indicate that CYP3A4 may not be the primary metabolic/elimination pathway for sorafenib. M2 was measurable in the absence of ketoconazole, but when sorafenib was co-administered with ketoconazole, M2 concentrations could not be measured, indicating that M2 formation *via* CYP3A4 was inhibited.

Warfarin
The effect of sorafenib on warfarin metabolism was assessed indirectly by measuring prothrombin time international normalized ratio (PT-INR) for patients treated with warfarin (pivotal phase III study; 11 patients in the sorafenib group, 10 patients in the placebo groups). The incidence rate of a 50% increase in PT-INR from baseline and a 100% increase in PT-INR from baseline, in patients on warfarin, were similar in the sorafenib vs. placebo groups. Mean percent maximum change in PT-INR ratios was lower in the sorafenib group vs. placebo group.

Omeprazol, dextromethorphan and midazolam
Substrates of CYP2C19, CYP2D6 and CYP3A4 were administered before and on the last day of a 28-day cycle with continuous administration of sorafenib 400 mg b.i.d to patients. There were no effects of sorafenib on omeprazol, dextromethorphan or midazolam plasma pharmacokinetics in this study.

Irinotecan
Following single intravenous infusions of 125mg/m^2 irinotecan together with 400 mg b.i.d. sorafenib to patients the exposure to the active metabolite of irinotecan (SN-38), increased approximately by a factor of 2, and there was a tendency to increased irinotecan exposure. Concomitant administration of 100 mg or 200 mg sorafenib b.i.d. did not result in significant changes in either irinotecan or SN-38. In a study involving 6 patients, irinotecan had no significant effect on sorafenib at the lower doses of sorafenib, but at 400 mg b.i.d. sorafenib + irinotecan 125 mg/m^2, sorafenib exposure increased by 68%

(90% CI 1.27-2.49). This was in a cohort of only 6 patients, and the Applicant suggests that the clinical relevance might be limited, given the relatively high variability of sorafenib.

Doxorubicin
In one group of patients (n=5) receiving 400 mg b.i.d. sorafenib, doxorubicin C_{max} and AUC increased by 103% (90% CI 1.27 - 3.26) and 47% (90% CI 1.18 - 1.81), respectively. In a larger cohort of patients (n=12) receiving 400 mg b.i.d. sorafenib the increase in doxorubicin AUC was 21% (90% CI 0.95 - 1.54). Mean AUC of sorafenib increased 22-36% at co-administration of doxorubicin with 100 or 200 mg b.i.d. sorafenib (n=5 per dose). There was no appreciable change in sorafenib AUC at 400 mg b.i.d. sorafenib.

Gemcitabine
Gemcitabine is rapidly converted by cytidine deaminase to deoxyfluorouridine (dFdU). Gemcitabine levels were too low to be adequately measured in the study evaluating concomitant treatment with gemcitabine and sorafenib. However, there were no effects of sorafenib on the metabolite dFdU, and no apparent effects of gemcitabine on sorafenib pharmacokinetics, but the variability in sorafenib concentrations was high.

Oxaliplatin
Oxaliplatin undergoes rapid non-enzymatic biotransformation. In small cohorts of patients receiving different doses of sorafenib together with oxaliplatin, there were no consistent changes in either sorafenib or oxaliplatin pharmacokinetics.

Discussion on clinical pharmacokinetics

Sorafenib was a low-solubility, high permeability compound. This was consistent with the finding that one single batch of 50 mg tablets exhibiting a slower *in vitro* dissolution rate compared to other batches of tablets had a lower bioavailability. *In vitro* studies indicated that sorafenib is a weak to moderate substrate of the efflux transporter P-gp. In cancer patients, across studies, the median T_{max} was approximately 3 hours (range 0-24 hours). Secondary absorption peaks were observed at 8-12 and 24 hours postdose, indicating enterohepatic re-circulation.

The absolute bioavailability is unknown. The bioavailability of the tablet was about 38%-49% of that of an oral solution. Doses below 100 mg (solution) and 400 mg (tablet), and b.i.d. dosing increased the bioavailability for tablets. The bioavailability was mainly limited by solubility. Solubility of sorafenib decreases at increased pH. The effect of anti-acidic medicinal products, such as antacids, H_2-antagonists or proton-pump inhibitors, on sorafenib bioavailability has not been studied. Decreased plasma concentrations of sorafenib cannot be excluded and, if possible, chronic treatment with anti-acidic drugs should be avoided during treatment with sorafenib (see SPC section 4.4 and 4.5). The applicant agreed to conduct, post-authorisation, a single dose, cross-over PK study in healthy volunteers to evaluate the effect of increased gastric pH (anti-acidic medication) on the bioavailability of sorafenib (400 mg, single dose).

Sorafenib bioavailability decreased with a high-fat meal, while there was no impact of a moderate-fat meal (approximately 30% of calories from fat) on sorafenib bioavailability compared to the fasted state. It is therefore recommended that sorafenib is administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before the meal or at least 2 hours after the meal, and should be swallowed with a glass of water (see SPC section 4.2).

Sorafenib is metabolised primarily in the liver and undergoes oxidative metabolism, mediated by CYP 3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide M 2, shows *in vitro* potency similar to that of sorafenib. This metabolite comprises approximately 9-16% of circulating analytes at steady state. The other active metabolites, M4 and M5, accounted for 8% and 6%, respectively, of the total exposure at steady state.

Most of the dose was absorbed and subsequently excreted, either as sorafenib or as metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in faeces but not in urine, indicating

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that biliary excretion of unchanged drug might contribute to the elimination of sorafenib (see section 5.2 of the SPC). Metabolites were mainly recovered in feaces and only in small amounts in urine. Metabolism and biliary excretion of unchanged drug was therefore the major elimination pathways for sorafenib. As some of the unchanged drug found in faeces could have been re-formed from excreted metabolites, the relative contribution of the two pathways could not be determined.

Across studies, there was no apparent relationship between creatinine clearance and sorafenib exposure, but no pharmacokinetic data for patients with moderate or severe renal impairment was presented (CLcrea<60 ml/min). However, since there is no renal excretion of unchanged sorafenib or M2, a significant effect of renal function on the exposure is not expected. A specific study in patients with renal impairment was not considered necessary, and no dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance >30ml/min). Appropriate information is included in the SPC (section 4.2 and 5.2). The SPC also states that no data is available in patients with severe renal impairment (creatinine clearance <30 ml/min) or in patients requiring dialysis.

Sorafenib pharmacokinetics in patients with mild to moderate hepatic impairment (Child-Pugh A and B) was investigated in a phase II study in patients with hepatocellular carcinoma. Exposure (calculated for 8 hours) was increased in Child-Pugh B compared with Child-Pugh A patients, but the difference was not statistically significant. There was no comparison with patients with normal hepatic function in this study, but exposure in both groups was within the range observed in other studies (e.g. AUC_{0-12} = 48 mg*h/ml in study 100277). The degree of metabolic impairment vs. degree of cholestatis was not discussed and the results cannot be extrapolated to cirrhosis patients. However, no dose adjustment is required in patients with mild to moderate hepatic impairment. Given the hepatic elimination of sorafenib, a further increase in exposure in patients with severe hepatic impairment would be expected (see SPC section 4.2, 4.4 and 5.2).

Analyses of demographic data suggested that there is no relationship between pharmacokinetics and age (up to 65 years) gender or body weight. Data in elderly were supported by safety data. No specific dosing recommendations were considered necessary based on these demographic criteria. The mean sorafenib exposure was lower in Japanese patients than in Caucasian patients, but the exposure was highly variable. The clinical relevance of this observation is unknown (see SPC section 5.2).
Substances that are inducers of enzyme activity (e.g. rifampicin, *Hypericum perforatum* also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may increase metabolism of sorafenib *via* CYP3A4 and UGT1A9 and thus decrease sorafenib concentrations. These drugs should only be administered concomitantly after careful benefit-risk evaluation (see SPC section 4.4 and 4.5). The results of a drug-drug interaction study with rifampicin will be provided post-authorisation. Ketoconazole, a potent inhibitor of CYP3A4, administered once daily for 7 days to healthy male volunteers did not alter the mean AUC of a single 50 mg dose of sorafenib. These data suggest that clinical pharmacokinetic interactions of sorafenib with CYP3A4 inhibitors are unlikely. Sorafenib inhibited CYP2C9 *in vitro*. It cannot be excluded that sorafenib may increase the concentrations of concomitantly administered substrates of CYP2C9. The concomitant treatment with sorafenib and warfarin, a CYP2C9 substrate, did not result in changes in mean PT-INR compared to placebo. However, patients taking warfarin or phenprocoumon should have their INR checked regularly. Sorafenib inhibited CYP2B6 and CYP2C8 *in vitro*, but the clinical relevance of this inhibition has not been evaluated. It cannot be excluded that sorafenib may increase the concentrations of concomitantly administered substrates of CYP2B6 (e.g. bupropion, cyclophosphamide, efavirenz, ifosfamide, methadone) and CYP2C8 (e.g. paclitaxel, amodiaquine, repaglinide). *In vitro*, sorafenib inhibited glucuronidation *via* UGT1A1 and UGT1A9. The clinical relevance of this finding is unknown (see SPC section 4.5). Caution is recommended when administering sorafenib with compounds that are metabolised/eliminated predominantly by UGT1A1 (e.g. irinotecan) or UGT1A9 pathway (see SPC section 4.4). Concomitant administration of sorafenib and midazolam, dextromethorphan or omeprazole, which are substrates for cytochromes CYP3A4, CYP2D6 and CYP2C19, respectively, did not alter the exposure of these agents. This indicates that sorafenib is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes. Therefore, clinical pharmacokinetic interactions of sorafenib with substrates of these enzymes were considered unlikely. CYP1A2 and CYP3A4 activities were not increased after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4. *In vitro*, sorafenib has been shown to inhibit the transport protein p-glycoprotein (P-gp). Increased

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plasma concentrations of P-gp substrates such as digoxin cannot be excluded at concomitant treatment with sorafenib (see SPC section 4.4 and 5.4). Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant treatment with sorafenib resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolised by the UGT1A1 pathway, there was a 67 - 120% increase in the AUC of SN-38 and a 26 - 42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see clinical efficacy section, and SPC section 4.4).

Pharmacodynamics

- Mechanism of action

Sorafenib was developed as an inhibitor of C-Raf (IC_{50} = 2 nM), but also inhibited wild type and mutant B-Raf (IC_{50} = 25 and 38 nM) *in vitro*. In addition, sorafenib inhibited the receptor tyrosine kinases for VEGFR-2, VEGFR-3, PDGFβ, c-KIT and FLT3. Based on in these properties, dual patterns of activity are possible: growth inhibition and anti-angiogenesis.

- Primary and secondary pharmacology

Primary pharmacology

There were no specific studies conducted in patients with RCC. Exploratory data were submitted from a single arm study conducted in patients with hepatocellular cancer (HCC). A number of biomarkers were explored, including phosphorylated ERK in tumour tissue, plasma HER-2/neu, plasma proteomics and blood cell RNA expression pattern. Higher intensity (immune histochemistry) of tumour pERK at baseline was correlated with longer time to tumour progression (p=0.00034, n=33). No correlation between baseline plasma HER-2/neu and response to sorafenib was seen. Twenty five proteomics components (mass spectroscopy) were found to differentiate between responders (PR, SD) and non-responders (PD). Based on data from 30 patients a panel of 18 genes was identified (Affymetrix GeneChip microarray) as differentiating between responders (PR, SD) and non-responders (PD).

To investigate the relationships between tumour levels of pERK and sorafenib associated patients outcome in RCC patients (study 11213), immunohistochemistry (IHC) was used to semi-quantitatively examine pERK levels in pre-treatment tumour biopsies. The maximum tumour staining intensity was graded on a standard IHC scale (neg = no staining, 1+ = weak staining, 2+ = moderate staining, 3+ = strong staining, 4+ = intense staining). The percent nuclei stained was assigned on a quartile basis (<5% = 0-5% nuclei stained, 1Q = 6-25% nuclei stained, 2Q = 26-50% nuclei stained, 3Q = 51-75% nuclei stained, 4Q = 76-100% nuclei stained). Paraffin-embedded tumour samples from 146 patients were subjected to pERK staining followed by pathologist's interpretation. Of these, appropriately prepared samples with sufficient material, pERK results, associated patient data, and antitumour activity data were available for only 125 patients (of the 903 subjects randomized in this trial). Patients were grouped based on percent nuclei expressing pERK (1Q *vs*. 2Q to 4Q), and also based on tumour staining intensity (Neg. to 3+ *vs*. 4+). These groupings separate those with high level staining from those with low level staining, and the ability to perform statistical analyses based on the numbers of samples available within each group. An analysis of PFS (using investigator assessed PFS) based on pERK staining is shown in table 6. Results related to survival were similar (data not shown).

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Table 6 - Analysis of PFS based on pre-treatment tumour pERK staining

	N	# Events	# Censored	Median PFS (Days)		Hazard Ratio (sorafenib/placebo)	
				Placebo	Sorafenib	Estimate	95% CI
Tumour % Expressing							
pERK % expressing unknown	776	506	270	84	168	0.53	(0.44, 0.63)
pERK % expressing 1Q	76	57	19	96	184	0.49	(0.29, 0.84)
pERK % expressing 2Q, 3Q, 4Q	49	41	8	84	126	0.66	(0.34, 1.25)
Tumour Staining Intensity							
pERK staining intensity unknown	776	506	270	84	168	0.53	(0.44, 0.63)
pERK staining intensity Neg, 1+, 2+, 3+	29	25	4	88	200	0.52	(0.23, 1.18)
pERK staining intensity 4+	96	73	23	86	166	0.59	(0.37, 0.94)

VEGF and sVEGFR-2 levels were analyzed in plasma samples from study 11213 using immunoassays. The results are presented in table 7.

Table 7: Analysis of PFS based on baseline plasma VEGF levels in patients from study 11213

Baseline VEGF Status	N	Median PFS (Days)		Hazard Ratio (sorafenib/placebo)		p-value*
		Placebo	Sorafenib	Estimate	95% CI	
VEGF ≤ 131 pg/mL	356	100	168	0.64	(0.49, 0.83)	0.096
VEGF > 131 pg/mL	356	83	167	0.48	(0.38, 0.62)	

* comparison of the hazard ratio of sorafenib to placebo between low-level and high-level baseline VEGF groups

Inactivating somatic mutations of the VHL gene are frequently found in RCC. The resulting inactivation of the VHL protein leads to an increase in tumour VEGF activity through upregulation of hypoxia-inducible factor-1α (HIF-1α). This increase in VEGF, mediated by VHL inactivation, leads to activation of VEGFR-2, which contributes to tumour angiogenesis. Given this relationship between VHL and angiogenesis, the relationship between VHL mutational status and sorafenib antitumour activity was investigated. DNA was isolated from formalin-fixed paraffin-embedded tumour samples, subjected to the polymerase chain reaction (PCR) in order to amplify each of the three exons encoding the VHL gene, and the amplified DNA was sequenced. A total of 141 samples from 134 patients had sequence data for at least 1 exon that could be utilized for analysis. Among the 48 subjects from whom all 3 exons were sequenced successfully, 15 (31.3%) had VHL mutations. Analysis of VHL mutational status and sorafenib antitumour activity is provided in the table below. The correlative analyses of mutational status and PFS or OS were performed assuming that all nucleotide changes in the VHL gene are equivalent.

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Table 8: Analysis of PFS based on VHL mutation status in a subset of patients in Study 11213

	N	# Events	# Censored	Median PFS (Days)		Hazard Ratio (sorafenib/placebo)	
				Placebo	Sorafenib	Estimate	95% CI
Exon 1							
No Mutation	90	72	18	79	166	0.55	(0.34, 0.89)
Mutation	26	20	6	45	165	0.39	(0.15, 1.04)
Missing	785	512	273	84	169	0.53	(0.45, 0.63)
Exon 2							
No Mutation	72	57	15	75	126	0.45	(0.26, 0.77)
Mutation	11	10	1	178	143	0.89	(0.24, 3.34)
Missing	818	537	281	84	169	0.54	(0.45, 0.64)
Exon 3							
No Mutation	88	68	20	84	126	0.62	(0.38, 1.00)
Mutation	3	3	0	141	402		
Missing	810	533	277	84	169	0.52	(0.44, 0.62)
Exon 1, 2 or 3*							
No Mutation	33	24	9	79	167	0.52	(0.23, 1.19)
Mutation	35	28	7	97	165	0.49	(0.22, 1.08)
Missing	833	552	281	84	168	0.54	(0.45, 0.63)

*patients that contained a mutation in any one exon were considered to have mutant VHL, even if one or more exons from that patient had not been sequenced. However, patients were only considered to have a wild-type VHL gene if all 3 exons had been successfully sequenced and all 3 exons contained no mutation.

Secondary pharmacology

Dermatologic events, including rash and hand-foot skin reaction, were the most common adverse events attributed to sorafenib in clinical studies (see clinical safety sections). Investigation of the association between clinical efficacy and dermatologic toxicity was based on PFS (according to investigator assessment in study 11213) analysis by presence or absence of rash and hand foot syndrome. The number of placebo patients with rash was 16% *versus* 40% in the sorafenib group. Median PFS in placebo patients with rash was 125 days *versus* 83 days in placebo patients without rash. PFS was analyzed for patients with or without a first report of rash in cycle 1 or 2. PFS was similar in patients receiving placebo who had a rash in cycle 1 or 2 (85 days) and those who did not have rash in cycle 1 or 2 (83 days), in patients receiving sorafenib PFS was 219 days in patients with a rash in cycle 1 or 2 vs. 164 days for patients with no rash in cycle 1 or 2. Analyses were also performed with PFS and hand-foot skin reaction. Hand-foot skin reaction was reported in 134 (29.7%) patients in the sorafenib group and 30 (6.7%) patients in the placebo group. Median PFS in sorafenib treated patients was found to be 181 days in patients with reaction *versus* 167 in those without.

Trough plasma sorafenib concentrations, defined as concentrations between 9 and 15 hours after administration of the previous dose, were evaluated as function of hypertension. Trough concentration data were evaluable in 67 patients of the 451 treated with sorafenib. Hand-foot skin reaction was reported in 10 (28.6%) patients with sorafenib concentrations < 3.2 mg/l and 12 (37.5%) patients with sorafenib concentrations ≥ 3.2 mg/l. Rash was reported in 9 (25.7%) patients with sorafenib concentrations < 3.2 mg/l and 9 (28.1%) patients with sorafenib concentrations ≥ 3.2 mg/l.
In a pooled analysis of 179 patients from 4 dose escalation studies, hand-foot skin reaction was reported in 45 (25%) patients and rash was reported in 32 (18%) patients. The frequency of dermatologic events correlated with dose and dermatologic events were most common in doses ≥ 400 mg bid.

In study 11213, hypertension was reported as an adverse event in 76 (16.9%) patients receiving sorafenib and 8 (1.8%) patients receiving placebo. Even in patients in whom hypertension was not reported as an adverse event, blood pressure tended to increase within the first 3 weeks of sorafenib therapy. Mean change in systolic blood pressure at day 21 of cycle 1 was 8.0 mmHg in sorafenib patients and 0 mmHg in placebo patients. The relationship between hypertension and efficacy was

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investigated based on investigator-assessed PFS data from study 11213 analyzed by blood pressure data (see also clinical safety section). Post-baseline hypertension [defined as systolic blood pressure (SBP) ≥ 160 mmHg] was reported in 170 sorafenib-treated patients and 73 patients receiving placebo (see table 9).

Table 9 - Progression-free survival analyzed by systolic blood pressure (SBP ≥ 160 mmHg)

Treatment Group	SBP ≥160 mmHg	N	Number Failed	Number Censored	Median PFS (Days)
Sorafenib	Yes	170	89	81	224
	No	270	176	94	139
Placebo	Yes	73	43	30	172
	No	356	273	83	78

Progression-Free Survival in sorafenib-treated patients was analyzed by presence or absence of hypertension in cycle 1. Trough concentration data were evaluable in only 67 patients of the 451 treated with sorafenib. Pharmacokinetic exposure and hypertension adverse events reported from in study 11213 were presented (data not shown). Measurements of circulating concentration of VEGF, catecholamines, epinephrine, norepinephrine, endothelin I, urotensin I, urotensin II, rennin, and aldosterone were performed at baseline and after 3 weeks of therapy. There were no significant changes in the levels of these vasoactive, renal, and angiogenic factors and there was no correlation of levels of these factors with blood pressure.

No PK/PD modelling data from the pivotal RCC study were provided. No pharmacodynamic interactions studies with other medicinal products or substances were conducted.

Discussion on clinical pharmacodynamics

The observation from the phase III study 11213 that baseline tumour pERK levels are not predictive of sorafenib antitumour activity in RCC patients complemented the results from an uncontrolled phase II study of sorafenib in RCC patients in which a lack of correlation was observed between pERK staining and time to progression (TTP) (n=64). Without control arm, it was not possible in a phase II trial to determine whether an observed correlation was predictive of sorafenib treatment efficacy or simply indicative of a prognostic baseline biomarker. Taken together, these limited phase II and phase III data suggested that baseline tumour pERK levels may not be prognostic in RCC patients nor predictive of sorafenib antitumour activity in RCC. In contrast, in a limited number of samples from an uncontrolled phase II study of sorafenib in hepatocellular carcinoma (HCC) patients, pERK staining intensity showed a significant correlation with TTP (n=33). Most patients assayed from study 11213 had similar pERK levels as described by the semi-quantitative 5-point scales utilized (i.e. >70% of patients had a maximum staining intensity of 4+, and almost 70% of patients had <50% of tumour cell nuclei stained). This lack of differentiation may represent a true lack of diversity among the RCC tumour population tested. Alternatively, the lack of differentiation may suggest that a finer scale of IHC quantitation is necessary in order to effectively differentiate sub-populations of RCC tumours.

Patients with either high baseline VEGF or low baseline VEGF benefited from sorafenib treatment. However, the data suggested poorer prognosis for patients with high baseline VEGF and a trend towards greater improvement in PFS for high VEGF subjects upon sorafenib treatment. Baseline levels of plasma sVEGFR-2 did not show a significant relationship to sorafenib treatment effect as measured by progression-free survival (PFS) or overall survival (OS). Mean plasma VEGF levels increased significantly from baseline to treatment cycle 1 day 21 and from baseline to treatment cycle 3 day 1 in the sorafenib-treated group (31.7% and 47.0% increase, respectively). Concurrently, mean sVEGFR-2 levels decreased significantly (17.8%, and 23.9%, respectively). No significant changes were observed for VEGF and sVEGFR-2 levels in the placebo group. Altogether, baseline VEGF did not appear as an important predictor of sorafenib activity. The applicant agreed to submit further data on biomarkers (including proteomics, metabolomics) post-approval.
Limited data suggest that DNA level tumour VHL mutational status is not predictive of sorafenib antitumour activity. These limited data did not support patient selection for sorafenib treatment based on this biomarker. The relationship between mutation and loss of VHL protein function has not yet been investigated. However VHL mutations have been reported as typifying for Clear Cell RCC, therefore “silent” mutations are unlikely to be common. Further analyses are ongoing to determine

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which of these nucleotide changes result in changes to the VHL protein, and, furthermore, which protein level changes may result in loss of VHL protein function. Amplification of receptors activating the MAPK pathway and mutations in MAPK pathway components associated with constitutive activation were not investigated.

For a multitargeted agent, a combination of signs and biomarkers, such as VEGF levels prior to and on therapy, might be needed to optimise the predictive value. Inhibition of angiogenesis has been associated with hypertension, particularly in patients treated with inhibitors of the vascular endothelial growth factor (VEGF) pathway [39].
The relationship between sorafenib exposure (dose, AUC, C_{max}) and response (inhibition of cellular proliferation, clinical toxicity, anti-tumour activity) were evaluated in phase I studies at doses of 100, 200, 300, 400, 600 and 800 mg bid. Increasing the dose from 400 to 600 mg bid did not increase the mean systemic exposure to sorafenib (13% in terms of $AUC_{(0-12),ss}$) yet significantly increased clinical toxicities. There was a trend towards increasing adverse events with dose, while there was no apparent relationship between steady state sorafenib $AUC_{(0-12),ss}$ or C_{max} values and the grade of drug-related adverse events at the 400 mg bid dose-level.
A relationship between dose and dermatologic events was observed. However, at the recommended dose (400 mg bid), the relationship between trough concentrations and skin reactions was weak. This observation was supported by plots of individual patient trough level data *versus* skin reactions (data not shown). The validity of the assessment of relationship between concentration and activity relies on the assumption that concentration data derive from samples taken prior to any dose reductions/interruptions. Rash (data from the two first treatment cycles), hypertension and higher trough levels in sorafenib treated patients was moderately predictive of prolonged PFS. This was not the case for hand-foot reactions. These observations were based on limited PK data.
There were no significant changes in the levels of vasoactive, renal, and angiogenic factors and there was no correlation of levels of these factors with blood pressure. A direct effect on the vasculature, possibly through endothelial cell function, was considered more likely than a humoral or renovascular mechanism for sorafenib-associated hypertension. Overall, considering the small sample size and the large number of patients who did not have PK samples collected, definitive conclusions on the predictive value of biomarkers could not be drawn. However, despite the large inter-individual variability in pharmacokinetics, no apparent relationship between exposure and dermatologic events, hypertension, or PFS was observed. Available systemic exposure data, although very limited, did not suggest any implications for the use of sorafenib in patients with renal cell carcinoma.

Clinical efficacy

- Dose response studies

Seven multiple dosing regimens/schedules studies were conducted. In these studies, 197 patients were exposed to sorafenib. The following schedules were investigated: 1 week on / 3 weeks off, 3 weeks on / 1 week off, 4 weeks on / 1 week off, once weekly to continuous dosing. Tolerability was used as activity marker aiming at defining a tolerated dose. Based on these data, 400 mg bid continuous dosing was proposed for the assessment of efficacy in the pivotal studies.

- Main studies

Two study reports of controlled clinical studies pertinent to the claimed indication were submitted.
Study 11213 was a phase III randomized, placebo-controlled trial to evaluate sorafenib in patients with advanced RCC who had received one prior systemic anticancer treatment [40].
Study 10039 was a phase II randomized, placebo-controlled discontinuation trial in patients with advanced, refractory solid tumours.

Study 11213

METHODS

Study Participants

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This was a randomised, placebo-controlled, multicentre clinical trial. The main inclusion criteria were adult patients with life expectancy ≥ 12 weeks; histologically or cytologically documented unresectable and/or metastatic measurable RCC (excluding rare subtypes of RCC, e.g. pure papillary cell tumour, mixed tumour containing predominantly sarcomatoid cells, Bellini carcinoma, medullary carcinoma or chromophobe oncocytic tumours); no more than one systemic therapy for advanced disease, during or after which the patient experienced disease progression (prior treatment must have been completed at least 30 days before but not more that 8 months prior to randomisation); at least 1 unidimensional measurable lesion by computed tomography (CT) scan or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumour (RECIST); risk rated "low" or "intermediate" according to Motzer score; performance status 0 or 1 according to Eastern Cooperative Oncology Group (ECOG) scale; total bilirubine < 4.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN, amylase and lipase < 1.5 x ULN, serum creatinine < 2.0 x ULN, prothrombin time (PT) and partial thromboplastin time < 2.5 x ULN.

Treatments

Patients were administered either sorafenib 400mg + best supportive care (BSC) or placebo + BSC twice daily on a continuous basis, without food or with a moderate fat meal. For the purpose of data recording, the treatment period was divided into 6-week cycles for the first 24 weeks; thereafter a cycle was defined as 8 weeks. Treatment continued until patients reached one of the criteria or withdrawal. Crossover from placebo at time of progression was not accepted.

Objectives

The primary objective was to evaluate the efficacy (survival) of sorafenib as compared with placebo. The secondary objectives were to evaluate the efficacy by progression-free survival (PFS), response rate (CR or PR), changes in health-related quality of life (HRQOL) and symptom response. Other objectives were duration of response, predictive value of pERK, HER-2, VEGF, plasma proteomics, gene expression profiling in blood cells and tumour biopsies.

Outcomes/endpoints

The primary outcome, overall survival, was defined as the time elapsed from randomization to death (from any cause). All randomized (ITT population) was included in the analyasis of the primary endpoint. Patients still alive at the time of the analysis were censored at their last date of follow-up.

The secondary outcome measures included PFS defined as the time from randomization to disease progression (radiological or clinical, whichever was earlier) or death (if death occurred before progression). Patients without tumour progression or death at the time of analysis were censored at their last date of tumour evaluation. PFS was primarily analysed by independent radiological review.

Estimate of the objective tumour response rates (confirmed CR and PR according to RESICT criteria) Confirmation scan for tumour responses assessed as CR or PR was to be conducted on day 1 of the next cycle, as long as it was at least 4 weeks after the first scan. The objective response rates were to be compared between treatment groups using Cochran-Mantel-Haenzel test adjusting for prognostic group (intermediate or low) and country.

Sample size

Sample size was based on the primary endpoint of overall survival. A clinically meaningful improvement was defined as a 33.3% increase in overall survival. Assuming a 2-sided α of 0.04, a total of 540 events are required to achieve 90% power if one interim and one final analysis are performed during this study.
The final analysis was to be performed (mature overall survival) when 540 events have been observed, if the stopping rule has not been met at the interim analysis.
The expected study duration was estimated at 29 months assuming patients enroll at a rate of 50 patients per month, an exponentially distributed event time, a 12 month median time for the control group and a 17 month long enrollment for a total of 856 subjects in the 2 treatment groups combined (428 subjects in each arm). Assuming a 3% rate for patients lost to follow-up, approximately 884 patients were to be randomized.

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About 270 deaths (number of events required for the first interim analysis on overall survival) were expected in about 17 months. The planned final analysis of the secondary PFS endpoint was to be performed when approximately 363 progressions were observed. This analysis, presented in this report, would have power of 90% to detect a 50% increase in PFS at the 1% significant level (two-sided). Assuming a median PFS for the control arm of 4.5 months, the 363 progressions were projected to occur in approximately 13 to 14 months from the initiation of the trial.

Randomisation

Randomisation (central) was stratified by country (19 countries, including 9 EU countries) and prognostic risk category according to Motzer criteria [poor ECOG (PS≥2), high serum lactate dehydrogenase (≥1.5xUNL), low serum hemoglobin, high corrected serum calcium (≥10 mg/dl), absence of prior nephrectomy].

Blinding (masking)

The active and placebo tablets were identical in appearance. Medication containers were labeled with unique bottle numbers, which were to be assigned to patients using the IVRS. Copies of an unblinded randomization code, in the form of individual sealed envelopes for each patient, were provided to each investigator. Envelopes could be opened by the investigator (preferably in consultation with a sponsor representative) if knowledge of a patient's treatment became necessary for the clinical management of that patient. Unblinding after disease progression for entry into the open-label phase of the study proceeded *via* the IVRS rather than with the blinded code envelopes.

Statistical methods

In the primary analysis, the two treatment groups was compared using a two-sided log-rank test with an overall α of 0.04 stratified by country and Motzer risk factor (see randomisation section). Kaplan-Meier survival curves were also to be displayed. An α spending function was to be used to account for interim analysis(es) to ensure that the overall false positive rate, α , is less that or equal to 0.04.
The planned final analysis on the secondary PFS endpoint was to be performed when approximately 363 progressions or deaths are observed.
The best overall response rates will be compared between treatment groups using the two-sided Cochran-Mantel-Haenszel test adjusting for country and Motzer risk category at the 0.05 α level.
Patient-reported outcomes (PRO) data were collected at day 1 of each cycle, and at the end of treatment visit, prior to seeing the physician. HRQOL assessment was based on two PRO instruments: the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI) to assess kidney cancer-related symptoms, and the Functional Assessment of Cancer Therapy-General (FACT–G). The primary endpoint was the longitudinal evolution of mean score over the first 5 treatment cycles. Treatment differences were evaluated by random coefficient. Treatment and Motzer score were factors, and relative day and baseline measure of the response variable were covariates in these models. Pattern mixture models were used to evaluate the robustness of the results from the random coefficient model.

RESULTS

Participant flow

At the time of the data cutoff for the PFS analysis, 976 patients were enrolled, 769 were randomized and 768 received at least 1 dose of study medication. All 769 patients were included in the ITT population, all but 1 patient were included in the safety population. There were 207 patients enrolled as of 28 January 2005 data cutoff date who were not randomized: 164 of these patients were screening failures (more than one prior therapy, prior therapy completed outside of the protocol window, brain metastases). The remaining 43 patients were still in screening as of the data cutoff date. Of the 768 patients treated, 384 (50%) were randomized to placebo and 384 (50%) to sorafenib. By the data cutoff date for the PFS analysis, 226 (58.9%) patients receiving placebo and 144 (37.5%) patients receiving sorafenib had discontinued treatment. The most common reason for discontinuing treatment are provided in table 10.

Table 10: Reasons for discontinuation of double blind therapy as per the investigator (randomised patients) – Study 11213

	sorafenib (n=384)	**placebo (n=385)**

Discontinued double blind therapy	**144 (37.5%)**	**226 (58.9%)**
Adverse events	13	14
Non-compliant with medication	0	1
Progression by clinical judgement	14	22
Radiological progression	103	174
Consent withdrawn	3	7
Lost to follow-up	1	4
Death	7	3
Missing	3	1

Conduct of the study

Six amendments of the protocol were made during the study. The first dealt with modifications to PFS analysis, survival analysis and biological modifiers, before patients were enrolled. The second included clarifications of the inclusion and exclusion criteria. Amendment 3 involved the monitoring of congenital nevi and histopathological effects of sorafenib on the skin. Amendment 4 involved functional imaging of tumour vascularisation. Amendment 5 was approved when 632 patients had been enrolled, and included the following revisions: clarification of timing and requirements for pre-study tumour tissue samples, correction of number of events required for analysis, clarification on reporting of adverse events and serious adverse events, and correction to exclusion criteria clarifying that patients may not have had previous therapy for RCC within the past 30 days but no longer than 8 months prior to randomisation. Amendment 6 was approved after all patients had been enrolled and specified that patients were to be unblinded and placebo patients would be given the opportunity to cross over to sorafenib.

Baseline data

Prior therapy for RCC Baseline, demographic and diseases characteristics are shown in table 11 and 12. About 80% of the study population received systemic therapy with palliative intent, about 20% adjuvant therapy. More than 70% of patients were less than 65 year old with good performance status and relatively good prognosis.

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Table 11 - Baseline demographic and diseases characteristics in study 11213 (ITT population)

Characteristics	sorafenib N = 384		placebo N = 385	
	n	(%)	n	(%)
Male	267	(69.5)	287	(74.5)
Female	116	(30.2)	98	(25.5)
Age Group, n (%)				
<65	255	(66.4)	280	(72.7)
≥65	127	(33.1)	103	(26.8)
ECOG Performance Status, n (%)				
0	184	(47.9)	180	(46.8)
1	191	(49.7)	201	(52.2)
2	6	(1.6)	1	(0.3)
Missing	3	(0.8)	3	(0.8)
Motzer Risk Factors, n (%)				
Low	200	(52.1)	194	(50.4)
Intermediate	184	(47.9)	191	(49.6)
RCC Subtype, n (%)				
Clear Cell	377	(98.2)	380	(98.7)
Papillary subtype	1	(0.3)	3	(0.8)
Other Variant	1	(0.3)	1	(0.3)
Missing	5	(1.3)	1	(0.3)
Duration of Disease (years)				
Mean (Range)	2.8	(0.1-19.4)	3.3	(0.1-19.9)
Median	1.6		1.9	
Duration of Metastatic Disease (years)				
Mean (Range)	1.3	(0.1-11.4)	1.3	(0-10.2)
Median	0.9		0.9	

Table 12 - Prior therapy for RCC in study 11213 (ITT population)

Characteristic	sorafenib N = 384		placebo N = 385	
	n	(%)	n	(%)
Type of Therapy				
Nephrectomy	356	(92.7)	362	(94.0)
Systemic Anticancer Therapy	381	(99.2)	382	(99.2)
Radiation Therapy	108	(28.1)	90	(23.4)
Type of Systemic Anticancer Therapy				
Interferon	260	(67.7)	264	(68.6)
Interleukin (IL-2)	168	(43.8)	170	(44.2)
Pyrimidine analogues	60	(15.6)	72	(18.7)
Vinca alkaloids	44	(11.5)	49	(12.7)
Progesterone agents	25	(6.5)	25	(6.5)
Investigational drugs	12	(3.1)	23	(6.0)
Intent of Systemic Anticancer Therapy				
Palliative therapy	315	(82.0)	304	(79.0)
Adjuvant therapy	65	(16.9)	80	(20.7)
Neoadjuvant therapy	2	(0.5)	5	(1.3)
Intent not reported	11	(2.9)	9	(2.3)
No palliative therapy	60	(15.6)	73	(19.0)
Intent of Cytokine Therapy				
IL-2 and/or Interferon, any Intent	319	(83.1)	313	(81.3)
Palliative IL-2 and/or Interferon	257	(67.2)	247	(64.2)
Adjuvant IL-2 and/or Interferon	58	(15.1)	66	(17.1)
Neoadjuvant IL-2 and/or Interferon	2	(0.5)	3	(0.8)
Intent not reported	8	(2.1)	8	(2.1)

Outcomes and estimation

Progression free survival

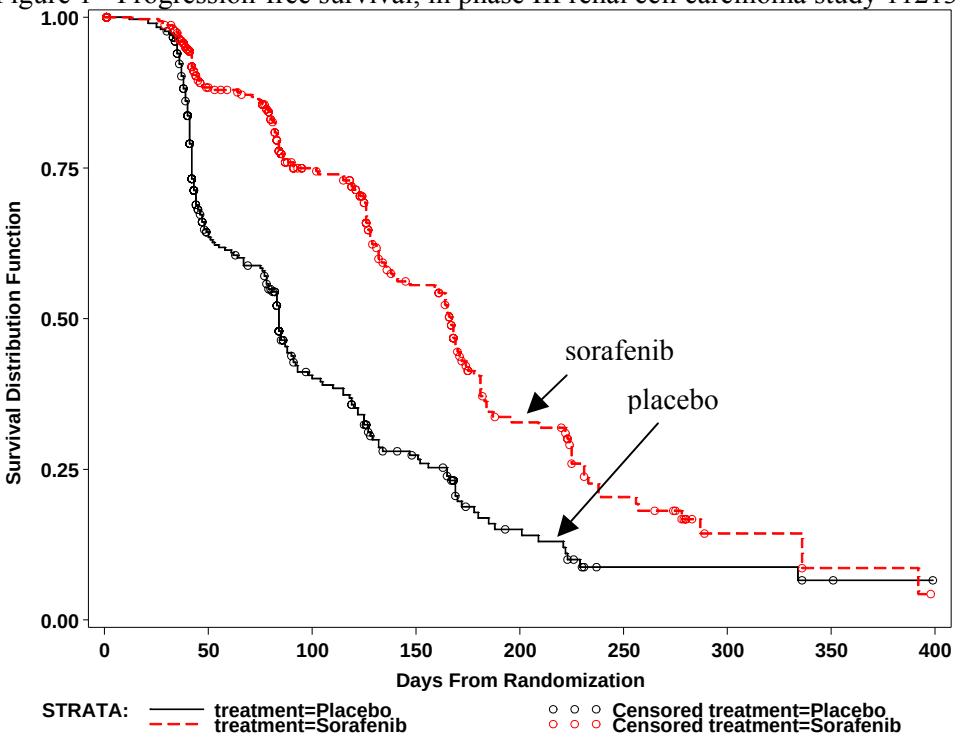
There were no meaningful differences in time from randomization to tumour evaluations (or scans) between the two treatment groups. The median time to first scan was 41 days for placebo and 42 days for sorafenib. The median time to the second scan was 84 days for both groups.

Median PFS was 84 days for patients randomised to placebo and 167 days for patients randomised to sorafenib. The stratified log-rank test had a two-sided p-value < 0.000001 (see table 13). The Kaplan-Meier curves for PFS by treatment group are shown in figure 1.

Table 13 - Progression-free survival, in phase III renal cell carcinoma study 11213

	sorafenib (N = 384)	**placebo (N = 385)**
Total failed	147 (38.3%)	195 (50.6%)
Total censored	237 (61.7%)	190 (49.4%)
Median PFS (days)	167	84
95% confidence interval for median	(139, 174)	(78, 91)
Hazard ratio (sorafenib/placebo)	0.44 (p<0.000001)	
95% confidence interval for hazard ratio	(0.35, 0.55)	

Figure 1 - Progression-free survival, in phase III renal cell carcinoma study 11213



Survival

First interim analysis (31 May 2005)

A total of 903 patients (451 in the sorafenib group and 452 in the placebo group) were enrolled in the study at the time of the survival analysis. The distribution of baseline demographics and patients characteristics was similar to that seen at the time of the PFS analysis conducted when 769 patients were enrolled. At the time of analysis there were a total of 220 deaths reported (123 in the placebo group and 97 in patients treated with sorafenib). The hazard ratio was 0.72 (p=0.018, two-sided log-rank, stratified by country and Motzer category; 95% CI: 0.55, 0.95). The median survival was 14.7 months in the placebo group. The median OS had not been reached for the sorafenib group.

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Response rate

As defined in the protocol, the first post-baseline tumour evaluation was performed at the end of cycle 1 (6 weeks post randomization). There were 97 patients (49 in the sorafenib group and 48 in the placebo group) randomized within 6 weeks of the data cut-off and consequently did not have the opportunity to undergo a post-baseline tumour evaluation. The status of patients with regard to analysis of tumour response is detailed in table 14.

Table 14 - Overall best confirmed tumour response in phase III renal cell carcinoma study 11213

Best Response	**sorafenib N = 335 n (%)**	**placebo N = 337 n (%)**
Complete response (CR)	0 (0)	0 (0)
Parcial response (PR)	7 (2.1)	0 (0)
Stable disease (SD)	261 (77.9)	186 (55.2)
Progressive disease (PD)	29 (8.7)	102 (30.3)
Not Evaluated	38 (11.3)	49 (14.5)

For the 7 patients treated with sorafenib with confirmed PR, the time to response ranged from 42 to 129 days with a median of 84 days. Four of the 7 responders had eventual disease progression with time to progression ranging from 84 to 252 days; the other 3 responders did not have progression at the time of the data cut off for this analysis.

- **Ancillary analyses**

Subgroup analyses – study 11213

Analysis of PFS based on independent radiological review by demographic, baseline and prognostic characteristics are shown in table15.

Table 15– Subgroup analysis of progression free survival (ITT population) – study 11213

					Hazard Ratio (sorafenib/placebo)		**Median PFS (days)**	
Variable	**Subgroup**	**N**	**Number of events**	**Number censored**	**Estimate**	**95% CI**	**placebo**	**sorafenib**
Sex	Male	554	255	299	0.45	(0.35, 0.58)	84	166
	Female	214	87	127	0.45	(0.29, 0.69)	83	169
Age	<65 years	535	245	290	0.49	(0.38, 0.63)	84	165
	≥65 years	230	97	133	0.34	(0.22, 0.52)	83	181
Motzer score	**Low**	**394**	**157**	**237**	**0.53**	(0.39, 0.73)	**91**	171
	Intermediate	**375**	**185**	**190**	**0.39**	(0.29, 0.53)	**61**	147
Nephrectomy	No	51	15	36	0.2	(0.06, 0.68)	83	225
	Yes	718	327	391	0.48	(0.38, 0.60)	84	166
Baseline ECOG	0	364	160	204	0.48	(0.35, 0.66)	88	172
	1	392	176	216	0.44	(0.32, 0.59)	67	147
Stage at study entry	**Stage III**	**26**	**12**	**14**	**0.91**	(0.27, 3.07)	83	126
	Stage IV	740	330	410	0.45	(0.36, 0.56)	84	168
Prior IL2/Interferon	No	137	52	85	0.35	(0.19, 0.63)	85	172
	Yes	632	290	342	0.47	(0.37, 0.60)	84	164
Prior palliative therapy	No	133	62	71	0.56	(0.33,0.93)	78	132
	Yes	636	280	356	0.43	(0.34,0.55)	84	169
Time since initial diagnosis >1.5 years	No	333	156	177	0.41	(0.30, 0.57)	76	147
	Yes	419	181	238	0.47	(0.35, 0.63)	92	170
Time since initial diagnosis to metastatic disease >0.5 year	**No**	**285**	**127**	**158**	**0.38**	(0.27, 0.55)	**79**	164
	Yes	**374**	**168**	**206**	**0.45**	(0.33, 0.61)	**84**	169

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Time since metastatic disease >1 year	No	411	193	218	0.42	(0.32, 0.57)	77	147
	Yes	339	143	196	0.46	(0.33, 0.65)	87	175
Top enrolling countries	France	186	114	72	0.47	(0.32, 0.68)	84	171
	US	**146**	**64**	**82**	**0.39**	(0.24, 0.65)	**76**	141
	Poland	**117**	**49**	**68**	**0.59**	(0.33, 1.05)	**122**	178

More favourable effects in terms of hazard ratios were observed in patients with more aggressive disease as indicated by early progression in the placebo group or by generally acknowledged risk factors (Motzer score "low" *vs*. "intermediate": median PFS for placebo group 91 *vs*. 61 days, HR 0.53 *vs*. 0.39; Time since initial diagnosis > 1.5 years, "yes" *vs*. "no": median PFS for placebo group 92 *vs*. 76 days, HR 0.47 *vs*. 0.41; Poland *vs*. United States: median PFS for placebo group 122 *vs*. 76 days, HR 0.59 *vs*. 0.39).

Survival second interim analysis (30 November 2005) - study 11213

At the time of analysis there were a total of 367 deaths reported and approximately 200 patients had crossed-over to sorafenib. The nominal alpha value for this analysis was 0.0094 (two-sided). The hazard ratio was 0.77 (p = 0.015, two-sided log-rank, stratified by country and Motzer category; 95% CI: 0.63, 0.95). The median survival was 19.3 months in the sorafenib group *vs.* 15.9 month in the placebo group). In the post-hoc subgroup analysis, the hazard ratio was 0.74 (95% CI: 0.57, 0.95) for Motzer score "intermediate" and 0.82 (95% CI, 0.57, 1.17) for Motzer score "low".
A pre-specified secondary analysis was performed in order to understand the potential effect of crossover on overall survival in placebo patients. In this analysis, survival data for placebo patients were censored at 30 Jun 2005, and data for sorafenib patients were those used in the primary analysis (30 Nov 2005). The latest survival data for sorafenib could be compared to the non-crossover placebo data. The hazard ratio was 0.74, p = 0.010.

Progression-free survival analysis (as off 31 May 2005) - study 11213

After the completion of the final PFS analysis in study 11213, independent reviews of radiologic studies were discontinued. The updated analysis was a descriptive analysis, which includes PFS data for all randomized patients as of 31 May 2005 (see table 16 and 17).

Table 16 - **Progression-free survival based on investigator assessment of radiological scans**

	sorafenib N=451	**placebo N=452**
Total Failed (n, %)	274 (60.9%)	330 (73.2%)
Total Censored (n, %)	176 (39.1%)	121 (26.8%)
Median PFS Days	168	84
Hazard ratio (sorafenib/placebo) (95% CI for hazard ratio)	0.51 (0.43, 0.60)	

Table 17- Analysis of investigator-assessed PFS as of 31 May 2005 by Motzer prognostic criteria

Prognostic Category	**HR (95% CI)**		**Median PFS (days)**	
			sorafenib	**placebo**
Low (n=460)	0.58	(0.46, 0.74)	181	97
Intermediate (n=441)	0.46	(0.36, 0.57)	166	64

- Analysis performed across trials (pooled analyses and meta-analysis)

There were no analysis performed across trials.

- Clinical studies in special populations

No studies were conducted to assess the efficacy of sorafenib in special population. No data were available in patients with impaired liver or kidney function.

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- Supportive study(ies)

Study 100391

This was a multicenter, placebo-controlled, randomised, discontinuation phase II study evaluating sorafenib in patients with advanced refractory cancer. The primary objective was to determine, in patients with advanced solid tumours and stable disease after 12 weeks of treatment with sorafenib, the percentage of patients who were progression-free after continued sorafenib treatment *versus* placebo. Patients should have refractory solid cancer for which other treatments were considered ineffective or intolerant, at least one measurable tumour lesion (modified WHO tumour response criteria), ECOG performance status 0 or 1, life expectancy of 12 weeks. Originally, the study focused on patients with colorectal carcinoma, but as tumour responses were observed in patients with RCC and without treatment options, this group of patients was expanded and 202 patients with RCC were included.
Treatment: Sorafenib 2 x 200 mg tablets bid. Dose modification due to toxicity allowed 200 mg bid and 200 mg QD. All patients were treated with sorafenib 400 bid for 12 weeks. Patients with stable disease at 12 weeks were to be randomised to placebo or continued sorafenib while responders continued on active therapy and patients with progressive disease went off study. The population for efficacy analysis was the ITT population, i.e. all patients who received at least 1 dose of study medication. The primary efficacy endpoint was progression-free rate at 12 weeks after randomisation. The two groups were compared using Cochran-Mantel-Haenszel test stratified by baseline ECOG score. Secondary endpoints included response rate (confirmed PR and CR).
A total of 187 patients with RCC completed 12 weeks of sorafenib therapy and 65 underwent randomised withdrawal while 79 continued open label sorafenib. Progression-free survival after randomisation in the placebo group was 41 days *vs.* 163 days in the sorafenib continuation group (p=0.0001). At 12 weeks post randomisation, 16/32 of the patients randomised to sorafenib were progression free *vs.* 6/33 in the placebo group (p = 0.008). Independent review of tumour response was undertaken in 152 patients and the partial response rate was 4% (8/202). Only 17 patients with CRC were included in the randomised withdrawal phase. Two out of 8 patients in the sorafenib group were progression-free 12 weeks after randomisation *vs*. 1/9 in the placebo group (p=0.14).

- Discussion on clinical efficacy

Based on the results of the dose finding studies, 400 mg bid continuous dosing was selected as the optimal schedule for the treatment with sorafenib. For a compound exhibiting predominantly features of a cytostatic, continuous dosing was considered appropriate [32, 41]. Biomarkers were not used to identify signs of anti-tumour activity in relation to dose or exposure. Skin reactions and diarrhoea were not dose limiting toxicities. After discussion and consultation of the oncology scientific advisory group, this was considered acceptable, due to the multi-targeting nature of sorafenib and the absence of biomarkers identified which may be used for dose adjustment (see discussion on clinical pharmacology). Further biomarker data derived from the pivotal study will be provided post-authorisation.

The application was based on a phase III, randomised, placebo-controlled trial including patients with advanced clear cell renal cell carcinoma, receiving sorafenib as a second line therapy, with good performance status and without impaired organ function. The primary endpoints of the study were overall survival and progression free survival (PFS), and according to the statistical analysis plan, a PFS analysis was undertaken after 363 events of progression or death.
While the conduct of interim analyses for overall survival (OS) could be accepted, the conduct of analysis of PFS prior to the final OS analysis is not recommended for studies designed to show a survival benefit.
Among randomised patients, 27% receiving sorafenib discontinued double blind therapy due to progression (independently reviewed and excluding clinical progression) *versus* 45% receiving placebo (95% CI for difference 12; 25%).
PFS results were statistically robust and median time to progression or death was prolonged in the sorafenib group (167 vs. 84 days). The pre-specified α for this analysis was 0.01, and the stratified log-rank test had a two-sided p-value < 0.000001. The estimated hazard ratio (risk of progression with sorafenib *versus* placebo) was 0.44 (95% CI 0.35, 0.55), representing a 56% reduction in hazard over placebo. Only considering independent imaging review data (and deaths), in the event analysis (and

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not timing of event), the difference between treatment groups was still convincing (95% CI for difference 11; 24%). Therefore no further sensitivity analyses were considered necessary.
The median difference in PFS in absolute terms was less than 3 months and after prolonged follow up the difference between treatment groups became small. This might illustrate that the activity expressed in terms of change in median is a poor measure of overall activity. More favourable effects were observed in terms of hazard ratios in patients with more aggressive disease as indicated by early progression in the placebo group. However, these differences were small and the interpretation of these data were limited by the small number of patients reported as having stage III disease and the small number of events among these patients. Due to the magnitude of the overall effect observed and the pattern of observed events, no major changes could be expected if late events had been recorded. No meaningful differences related to age and gender were observed.

A total of 903 patients (451 in the sorafenib group and 452 in the placebo group) were enrolled in the study at the time of the first survival analysis. A total of 220 deaths were reported (123 in the placebo group and 97 in patients treated with sorafenib). The hazard ratio was 0.72 (p=0.018, two-sided log-rank, stratified by country and Motzer category; 95% CI: 0.55, 0.95). The formal alpha level for this analysis was 0.0005. The survival analysis was thus non-significant. Survival data as of November 2005 were still considered immature (367 deaths in 903 patients). Results remained stable comparing data from the first cut-off date. Formally the results were still statistically non-significant in relation to the stopping criteria for interim analyses. However, based on PFS data, it was concluded that a favourable and clinically meaningful effect has been demonstrated.

A final analysis of OS will be conducted when approximately 540 deaths are observed. However, it is anticipated that the crossover of placebo patients form placebo to sorafenib arm after May 2005, may limit interpretation of the results.

It was considered unfortunate that the blind was broken and that patients were crossed-over based on PFS data, as survival results were expected to be either immature or highly confounded by cross-over to active therapy. It was anticipated that a good estimate of the survival benefit would be hard to obtain. However, after consultation of the oncology scientific advisory group, the CHMP considered that PFS *per se* could be considered as a measure of the clinical benefit of sorafenib. Based on PFS data, it was concluded that a favourable and clinically meaningful effect has been demonstrated.

The analysis of an enrichment study design (all patients were treated with sorafenib 400mg bid; patients with stable disease at 12 weeks were randomised to placebo or sorafenib; responders continued on active open label therapy; patients with progressive disease went off study) confirmed the activity of sorafenib in patients with advanced RCC and that the activity is mainly cytostatic, i.e. growth inhibiting. The methodology for assessing quality of life was considered adequate and the results (data not shown) suggested a possible advantage for the patients treated with sorafenib, to be weighed against an increased incidence of side effects.

Sorafenib is not recommended for use in children and adolescents due to a lack of data on safety and efficacy (see SPC sections 4.2 and 5.3).

Clinical safety

- Patient exposure

Safety data for sorafenib have been derived from six completed phase I single-agent studies (studies 10658, 10164, 100277, 100283, 100313, and 100342), one ongoing extension study (10922), two phase II studies (100391 and 10874) and one phase III study (11213). Adverse events were reported by the investigators as an investigator term, and as a term in the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) coding dictionary. An integrated safety analysis of data from phase I and II clinical studies was provided, with safety data presented in MedDRA, based on the investigator text terms provided.
A total of 1872 patients with cancer and 85 healthy volunteers were exposed to sorafenib as of 31 Dec 2004 in sponsor-initiated trials, thereof 1376 patients were exposed to single agent sorafenib. There were 1219 patients exposed to sorafenib in completed single agent studies with 253 patients being exposed for at least 6 months and 42 patients being exposed for at least 1 year (data cut-off

January 2005). The patient exposure to sorafenib in the pivotal trial are provided in table 18 and 19. There was no specific treatment for sorafenib overdose.

Table 18 - Exposure to sorafenib in completed single agent studies

	any exposure	**≥ 6 months**	**≥ 12 months**
Phase I	197[a]	33	13
Phase II[c]	638[b]	135	23
Phase III[d]	384[b]	85	6
Total	1219	253	42

a: 41 patients received sorafenib 400 mg bid; b: All patients received sorafenib 400 mg bid; c: At the time of the analysis of the two studies in the phase II pool, 86 patients were still receiving sorafenib; d: At the time of the PFS analysis in study 11213, 158 patients were still receiving sorafenib.

Table 19 - Duration of exposure in study 11213

Duration of Treatment	**As of 28 Jan 2005**		**As of 31 May 2005**	
	sorafenib N=384	**placebo N=385**	**sorafenib N=451**	**placebo N=452**
N	329	326	447	443
Range (weeks)	0.7-57.0	0.0-57.1	0.7-72.3	0.4-76.1
Mean (weeks)	19.4	13.4	25.4	15.5
SD (weeks)	13.0	10.6	16.1	12.6
Median (weeks)	18.0	9.2	23.3	12.0

n = number of patients with duration of exposure data available; N = total number of patients; SD, standard deviation

- Adverse events

Study 11213 (data cut-off of 31 May 2005)

A total of 902 patients, including 451 receiving sorafenib were involved in the safety analyses. Study medication was discontinued during double blind therapy due to adverse events in 46 patients in the sorafenib arm and 37 patients in the placebo arm. A total of 121 patients continued to receive open label sorafenib after disease progression. At the time of the safety analysis, 12 patients had crossed-over to sorafenib. An overview of safety events in study 11213 is provided below.

Table 20- Overview of safety events in study 11213

Event	**As of 28 Jan 2005**				**As of 31 May 2005**			
	sorafenib[a] N=384		**placebo[a] N=384**		**sorafenib[b] N=451**		**placebo[b] N=451**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Treatment-emergent adverse event	325	(84.6)	283	(73.7)	428	(94.9)	387	(85.8)
Drug-related adverse event	282	(73.4)	171	(44.5)	375	(83.1)	229	(50.8)
Serious adverse event	91	(23.7)	68	(17.7)	153	(33.9)	110	(24.4)
Drug-related serious adverse event	25	(6.5)	10	(2.6)	35	(7.8)	12	(2.7)
Adverse event leading to permanent discontinuation	24	(6.3)	28	(7.3)	46	(10.2)	37	(8.2)
Deaths within 30 days of receiving study medication	23	(6.5)	18	(4.7)	48	(10.6)	28	(6.2)

a: The median treatment duration was 9 weeks for the placebo group and 18 weeks for the sorafenib group; b: The median treatment duration was 12.0 weeks for the placebo group and 23.1 weeks for the sorafenib group; n = number of patients with event; N = total number of patients in the group.

The most common drug reactions are reported in the table below. Cumulative event rates by 6-week cycles indicate that most of adverse reactions were reported already in cycle 1. An increase over time was seen for alopecia 9% cycle 1, > 20% cycle 3+, neuropathy 6% and 10%, and hypertension 6% and 10%.

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Table 21: Adverse drug reaction reported in at least 5% of patients in any treatment group

MedDRA terms		sorfenib (N=451)			placebo (N=451)		
System organ class	**Preferred Term**	**all grades**	**grade 3**	**grade 4**	**all grades**	**grade 3**	**grade 4**
Metabolism and Nutrition Disorders	anorexia	9%	<1%	0%	5%	<1%	0%
Nervous System Disorders	headache	6%	0%	0%	3%	0%	0%
Vascular Disorders	hypertension	12%	2%	<1%	1%	<1%	0%
	flushing	6%	0%	0%	2%	0%	0%
Gastrointestinal Disorders	diarrhoea	38%	2%	0%	9%	<1%	0%
	nausea	16%	<1%	0%	12%	<1%	0%
	vomiting	10%	<1%	0%	6%	<1%	0%
	constipation	6%	0%	0%	3%	0%	0%
Skin and Subcutaneous Tissue Disorders	rash	28%	<1%	0%	9%	<1%	0%
	alopecia	25%	<1%	0%	3%	0%	0%
	hand foot syndrome	19%	4%	0%	3%	0%	0%
	pruritus	17%	<1%	0%	4%	0%	0%
	erythema	15%	0%	0%	4%	0%	0%
	dry skin	11%	0%	0%	2%	0%	0%
	skin exfoliation	7%	<1%	0%	2%	0%	0%
Musculoskeletal, Connective Tissue and Bone Disorders	arthralgia	6%	<1%	0%	3%	0%	0%
	pain in extremity	6%	<1%	0%	2%	0%	0%
General Disorders and Administration Site conditions	fatigue	15%	2%	0%	11%	<1%	0%
	asthenia	9%	<1%	0%	4%	<1%	0%

Haemorrhage: Bleeding events were more commonly reported in sorafenib treated patients (15% *versus* 8%), thereof events grade 3 and more in 2.5% vs. 1.7%.

Wound healing: there was no indication that wound-healing was affected by sorafenib monotherapy, but only 70 patients on sorafenib underwent surgical procedures, mainly minor. No formal studies of the effect of sorafenib on wound healing have been conducted.

Thromboembolism: The overall incidence of treatment related cardiac ischemia/infarction events was higher in the sorafenib group (2.9%) than in the placebo group (0.4%).

Neuropathy: Sensory neuropathy was more commonly reported in sorafenib treated patients (13.1%) than in the placebo group (6.4%).

Exploratory studies

The sorafenib dose received by patients involved in phase I trials (n=197) ranged from 100 bid to 800 bid. The rate of drug-related adverse reactions increased with higher doses of sorafenib. In particular, the incidence of diarrhoea, nausea, and stomatitis were higher in patients receiving 800 mg bid than in patients receiving 400 mg bid. Similarly, drug-related hand-foot skin reactions were reported in no patients at 100 mg bid, 11.8% at 200 mg bid, 12.2% of patients at 400 mg bid, 27.5% at 600 mg bid and 30.8% at 800 mg bid.
In the phase II trials, 91.8% of the adverse events were considered related to sorafenib. The most common drug-related adverse events were rash (38.4%), diarrhoea (37.5%) and hand-foot syndrome (35.0%). Drug-related hypertension had an incidence of 16.8%.

- Serious adverse events and deaths

Study 11213 (data cut-off of 31 May 2005)

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Table 22: Grade 3 and 4 adverse drug reaction reported in at least 2% of patients

NCI-CTCAE Category/Term	sorafenib (N=451)				placebo (N=451)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	n	(%)	n	(%)	n	(%)	n	(%)
Any event	139	(30.8)	32	(7.1)	97	(21.5)	27	(6.0)
Blood/bone marrow								
Decreased hemoglobin	9	(2.0)	3	(0.7)	16	(3.5)	4	(0.9)
Cardiovascular, general								
Hypertension	**15**	**(3.3)**	**1**	**(0.2)**	**2**	**(0.4)**	**0**	**(0.0)**
Constitutional symptoms								
Fatigue	21	(4.7)	1	(0.2)	14	(3.1)	2	(0.4)
Dermatology/skin								
Hand -foot skin reaction	**25**	**(5.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Gastrointestinal								
Diarrhoea	11	(2.4)	0	(0.0)	3	(0.7)	0	(0.0)
Pain								
Pain, tumour pain	**13**	**(2.9)**	**0**	**(0.0)**	**7**	**(1.6)**	**1**	**(0.2)**
Pain, bone pain	2	(0.4)	1	(0.2)	14	(3.1)	1	(0.2)
Pulmonary								
Dyspnea	12	(2.7)	4	(0.9)	10	(2.2)	1	(0.2)

N: number of patients with event; N: total number of patients in the group; CTCAE: Common terminology criteria for AE

The incidence of deaths within 30 days of study drug was higher in the sorafenib group (48 patients, 10.6%) than in the placebo group (28 patients, 6.2%). Patients who were treated with sorafenib had the option of continuing sorafenib therapy after progression of disease, while cross-over was not permitted in patients progressing on placebo. Most deaths in both treatment groups were due to progressive disease.

Exploratory trials

In phase II trials, 40.1% of adverse events were grade 3 or 4 events. Grade 3 hypertension was reported in 95 (14.9%) patients and assessed as drug-related in 75 (11.8%). There was one Grade 4 hypertension, which was reported as hypertensive crisis and related to sorafenib. In addition to hypertension, Grade 3 events that occurred in at least 5% of patients included diarrhoea (5%), dyspnoea (5.3%) and hand-foot syndrome (7.5%), with an overall incidence of Grade 3 events of 51.6%. The most common Grade 4 events in the phase II database included dyspnoea (1.1%), increased bilirubin (0.9%), asthenia (0.8%), increased GGT (0.8%), anaemia (0.6%) and abdominal pain (0.6%), with an overall incidence of Grade 4 events of 12.1%. One patient involved in phase II trial had a drug-related adverse event (cerebrovascular ischemia) leading to death.

- Laboratory findings

Study 11213 (data cut-off of 31 May 2005)

A central laboratory was used to evaluate hematological and biochemical parameters. The Grade 3 and 4 laboratory abnormalities occurring at a higher rate (≥ 2%) in sorafenib vs. placebo patients were lymphopenia, neutropenia, elevated lipase, and hypophosphatemia (see Table 23). Sorafenib modestly suppresses bone marrow function.

Table 23: Grade 3 or 4 laboratory abnormalities observed in ≥ 2% of patients

CTCAE Category/Term	sorafenib (N = 451)				placebo (N = 451)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	n/N[a]	(%)	n/N[a]	(%)	n/N[a]	(%)	n/N[a]	(%)
Blood/bone marrow								
Low Leukocytes	11/434	(2.5)	0/434	(0.0)	4/425	(0.9)	0/425	(0.0)
Lymphopenia	52/434	(12.0)	3/434	(0.7)	29/424	(6.8)	2/424	(0.5)
Low Neutrophils	12/434	(2.8)	11/434	(2.5)	6/424	(1.4)	4/424	(0.9)
Low Hemoglobin	8/434	(1.8)	1/434	(0.2)	11/425	(2.6)	4/425	(0.9)

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CTCAE Category/Term	sorafenib (N = 451)				placebo (N = 451)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	n/N[a]	(%)	n/N[a]	(%)	n/N[a]	(%)	n/N[a]	(%)
Low Platelets	2/433	(0.5)	1/433	(0.2)	0/425	(0.0)	0/425	(0.0)
Coagulation								
Prolonged INR	23/435	(5.3)	0/435	(0.0)	28/425	(6.6)	0/425	(0.0)
Metabolic/laboratory								
Hypophosphatemia	58/436	(13.3)	0/436	(0.0)	11/427	(2.6)	0/427	(0.0)
Elevated lipase	50/436	(11.5)	4/436	(0.9)	22/427	(5.2)	8/427	(1.9)
Hyponatremia	25/436	(5.7)	3/436	(0.7)	20/427	(4.7)	0/427	(0.0)
Hyperglycemia	14/436	(3.2)	1/436	(0.2)	22/427	(5.2)	1/427	(0.2)
Hyperkalemia	15/436	(3.4)	7/436	(1.6)	11/427	(2.6)	3/427	(0.7)
Elevated amylase	6/436	(1.4)	0/436	(0.0)	9/427	(2.1)	3/427	(0.7)
Hypercalcemia	1/436	(0.2)	3/436	(0.7)	6/427	(1.4)	8/427	(1.9)
Hypocalcemia	7/436	(1.6)	4/436	(0.9)	0/427	(0.0)	2/427	(0.5)

n = number of patients with the laboratory abnormality, N = total number of patients with the laboratory measurement reported; INR – international normalized ratio.

Increased lipase and amylase were very commonly reported and grade 3 or 4 lipase elevations occurred in 11% of patients in the sorafenib group compared with 7% of patients in the placebo group. Grade 3 or 4 amylase elevations were reported in 3% of patients in the sorafenib group compared to 1% of patients in the placebo group. Three cases of pancreatitis were reported in the sorafenib group *versus* one in the placebo group.

Hypophosphatemia, was observed in 45% of sorafenib patients and 12% of placebo patients had hypophosphatemia. There were no cases of Grade 4 hypophosphatemia, defined as below 1.0 mg/dl. Grade 3 hypophosphataemia (1 - 2 mg/dl) occurred in 13% on sorafenib treated patients and 3% of patients in the placebo group. The aetiology of hypophosphataemia associated with sorafenib could not be defined.

- Safety in special populations

As of 28 January 2005, 703 men and 266 women (approximately reflecting the prevalence of the disease) were treated with sorafenib. Hypertension, rash, hand-foot syndrome and alopecia tended to be reported in a higher frequency in women.

The majority of patients included in the clinical trials were between 45 and 64 years of age. There were no signs of an increased incidence of peripheral neuropathy in the elderly. Hypertension was reported in about 40% (53/128) of patients in the age group 45-64 and 25% (14/56) in those over 65 years. Nine of the 202 RCC patients in study 100391 (4.4%) and 32 of the 902 patients in study 11213 (3.5%) were ≥ 75 years of age. Although no renal toxic effects of sorafenib have been identified, there were 3 (16.7%) patients ≥75 years in the sorafenib group and none in the placebo group who had renal failure reported as an adverse event. Overall, renal failure was reported as an adverse event in 10 (2.2%) sorafenib patients and 4 (0.9%) placebo patients in study 11213.

Too few non-Caucasians were included in clinical trials to draw conclusion on safety in different ethnic groups. No safety data in patients with hepatic and renal impairment were submitted. The safety of sorafenib in paediatric patients has not been studied.

- Safety related to drug-drug interactions and other interactions

No specific studies were conducted to assess the safety related to drug-drug interactions. Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy.

- Discontinuation due to adverse events

As of 31 May 2005, 97 patients treated with sorafenib had at least one dose interruption due to adverse events. Most common reasons for temporary discontinuation of sorafenib were hand foot skin reaction (22 patients) and diarrhoea (15 patients). In total, dose reductions due to adverse events were reported

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in 58 sorafenib patients. The most common events leading to dose reductions were hand foot skin reaction (24 patients) and diarrhoea (10 patients). Hypertension led to dose interruption in 8 patients and dose reduction in 5 patients treated with sorafenib. Adverse events led to dose interruption in 27 patients receiving placebo and dose reduction in 14 patients receiving placebo. The most common reasons for dose reductions and interruptions in placebo patients were pain and diarrhoea.

- Post marketing experience

No post-marketing experience was available at the time of submission.

- Readability testing

The package leaflet was submitted to a pilot testing (involving four subjects) as well as two separate full rounds of user testing involving 10 subjects each. The package leaflet used in these testing rounds did not significantly differ from the version revised due to the scientific assessment.

- Discussion on clinical safety

Code terms in the NCI-CTC (National Cancer Institute Common Toxicity Criteria) and MedDRA dictionaries were used. Investigators provided both an investigator term and a CTC coded term for each event. The potential assignment of different CTC and MedDRA codes to the same event was acknowledged. However, NCI-CTC are commonly used in oncology trials. Terms were translated into MedDRA and the approach was considered acceptable by the CHMP.
The safety evaluation of sorafenib was based on 1286 patients who received sorafenib in single agent clinical studies. The most common drug-related adverse events were diarrhoea, rash, alopecia and hand-foot skin reaction. Events coded as drug related were reported in 80% of sorafenib treated patients *versus* 50% in the placebo group. Rash and hand-foot skin reaction were usually CTC Grade 1 and 2 and generally appeared during the first six weeks of treatment with sorafenib. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib (see section 4.4 and 4.8 of the SPC).
The events most commonly associated with permanent discontinuation of study drug were pulmonary events (9 patients in sorafenib group, 4 patients in placebo group), gastrointestinal events (8 patients in sorafenib group, 4 patients in placebo group), and constitutional symptoms (7 patients in sorafenib group, 3 patients in placebo group). An increased risk of bleeding may occur following sorafenib administration. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of sorafenib should be considered (see section 4.4 and 4.8 of the SPC).

Altogether 97 sorafenib patients had at least one dose interruption, thereof 22 due to hand-foot skin reactions and 10 due to diarrhoea. Most of these patients had a dose reduction upon resumption of therapy. Hypertension led to dose interruption in 8 patients and dose reduction in 5 patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of sorafenib should be considered (see section 4.4 and 4.8 of the SPC).
Treatment related cardiac ischaemia/infarction adverse events was higher in the sorafenib group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from the pivotal study. Temporary or permanent discontinuation of sorafenib is recommended in patients who develop cardiac ischemia and/or infarction (see section 4.4 and 4.8 of the SPC). Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, International Normalized Ratio (INR) or clinical bleeding episodes (see section 4.4 and 4.8 of the SPC).

In the pivotal trial, more adverse events were reported as of 31 May 2005, mainly due to prolonged follow-up. There were about 10% (absolute) more serious adverse events in the sorafenib group and 4% more deaths within 30 days of receiving study medication. The median duration of therapy in sorafenib patients increased from 18.0 weeks as of 28 Jan 2005 to 23.3 weeks as of 31 May 2005. The overall exposure was longer in the sorafenib group (218.3 patient-years) than in the placebo group

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(132.0 patient-years). The increase in the rate of adverse events in the sorafenib arm was also explained by the continuation of sorafenib therapy in the setting of tumour progression, as per the protocol. Patients on placebo were to discontinue therapy upon progression (until the crossover was instituted in April 2005). Patients with progressive disease were expected to have a higher rate of adverse events.

In phase I and phase II trials, common and drug related adverse reactions were dose-dependent and the overall pattern of adverse events was similar to that in the phase III trial.
No data was available on patients with Child Pugh C (severe) hepatic impairment. Since sorafenib is mainly eliminated *via* the hepatic route, a special warning has been included in section 4.4 of the SPC as exposure might be increased in patients with severe hepatic impairment. Temporary interruption of sorafenib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. Cases of renal failure have been reported in elderly patients. Monitoring of renal function is recommended in these patients (see section 4.4 od the SPC). There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. The decision to resume sorafenib therapy following a major surgical intervention should be based on clinical judgement of adequate wound healing (see SPC section 4.4). High risk patients, according to MSKCC (Memorial Sloan Kettering Cancer Center) prognostic group, were not included in the pivotal study and the benefit-risk balance in these patients has not been evaluated.

The highest dose of sorafenib studied clinically was 800 mg twice daily. The adverse events observed at this dose were primarily diarrhoea and dermatological events. In the event of suspected overdose, it is recommended that sorafenib is withheld and supportive care instituted, where necessary (see SPC section 4.9). No studies on the effects on the ability to drive and use machines have been performed. There is no evidence that sorafenib affects the ability to drive or to operate machinery (see SPC section 4.7). Sorafenib is contra-indicated in patients with hypersensitivity to the active substance or to any excipients (see SPC sections 4.3).
Hypophosphatemia was a commonly observed phenomenon in patients treated with sorafenib and has been reported also for other tyrosine kinase inhibitors (e.g. imatinib, erlotinib). The mechanisms behind this adverse reaction will be investigated post-authorisation.

1.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table 24: Summary of the risk management plan

Potential Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Dermatological toxicities	-Routine pharmacovigilance activities -In cases of Steven-Johnson or Lyell syndrome, a targeted questionnaire to direct data collection on SAE's	-Warning in section 4.4 of the SPC that dermatological side effects occur generally during the first 6 months of treatment with Nexavar -Management of symptoms by topical therapy -Temporary treatment interruption or dose reduction -In severe cases permanent discontinuation of sorafenib is recommended -Listed as ADR's in Section 4.8 of the SPC
Hypertension	-Routine Pharmacovigilance activities -Additional clinical AE data collection from ongoing clinical studies. -A targeted questionnaire to direct data collection on SAEs reported as hypertensive crisis will be used.	-Warning in section 4.4 of the SPC that Regular blood pressure should be monitored and treated by standard medical practice, required. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of Nexavar should be considered. -Listed as ADR in section 4.8 of the SPC
Increases in lipase, amylase and symptomatic pancreatitis.	-Routine Pharmacovigilance activities -Additional clinical AE data collection from ongoing clinical studies. -Key Bayer sponsored clinical studies will continue to collect lipase and amylase data -SAE questionnaires will be used to collect data for ---SAE reports of significant lipase and amylase increases and clinical	-Listed as ADR's in section 4.8 of the SPC and data described in section 4.8 on laboratory test abnormalities

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Potential Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	pancreatitis. -A review will be performed to determine the rates of lipase and amylase increases, the incidence of pancreatitis in cancer patients and to assess the sensitivity and specificity of the relationship between biochemical and clinical sequelae	
Hypophosphataemia	-Routine Pharmacovigilance activities: -Additional clinical AE data collection from ongoing clinical studies. -A study will be conducted to understand the mechanism of hypophosphataemia. -Additionally, attempts will be made to evaluate mutations in the tyrosine kinase domain of the FGF Receptor 3 to perform correlative analysis with hypophosphataemia. -Results expected to be available in Q 2/2008	-Listed as ADR in section 4.8 of the SPC
Haemorrhage	-Routine Pharmacovigilance activities -Additional clinical AE data collection from ongoing clinical studies. -In the planned Phase 3 non-small cell lung cancer (NSCLC) trial case record forms will collect histological subtype of the tumour (squamous vs. adeno carcinomas) -Specific SAE follow up, using SAE questionnaires for: - - Cerebral hemorrhage. - Significant lung bleeding -Epidemiological assessment - To determine in the advanced or metastatic RCC population the rates of cerebral bleeding, outcome of cerebral bleeding, prevalence of cerebral metastasis and cerebral bleeding from these metastases. - To determine the risk factors for and the incidence of haemoptysis and significant lung bleeding in the NSCLC population. - To assess bleeding rates across tumour types to highlight particular disease settings at higher risk of bleeding	-Warning in section 4.4 of the SPC that an increased risk of bleeding may occur following Nexavar treatment. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of Nexavar should be considered -Listed as ADR in section 4.8 of the SPC
Arterial thrombosis / Cardiac ischaemia and/or infarction	-Routine Pharmacovigilance activities -Additional clinical AE data collection from ongoing clinical studies. -Further assessment of the available epidemiological resources will be made to determine the rates of cardiovascular and cerebrovascular diseases in relevant cancer patient populations. -Specific SAE questionnaires on Myocardial infarction and cerebrovascular ischemic events will be used.	-Warning in section 4.4 of the SPC that in a randomised, placebo-controlled, double-blind study the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the Nexavar group (2.9%) compared with the placebo group (0.4%). Temporary or permanent discontinuation of Nexavar should be considered in patients who develop cardiac ischemia and/or infarction -Cardiac ischemia and/or infarction are listed as ADR in section 4.8 of the SPC
Wound healing complications	-Routine Pharmacovigilance activities -Additional clinical AE data collection from ongoing clinical studies. -SAE reports of surgical interventions will be followed up to query whether the investigator/ prescriber consider there to have been any adverse effects on wound healing. -When company sponsored adjuvant or neo adjuvant clinical trials are planned, appropriate data collection techniques will be defined to capture any effects on wound healing and scar formation.	-Warning of section 4.4 of the SPC that no formal studies of the effect of sorafenib on wound healing have been conducted and limited clinical experience is available regarding the timing of reinitiation of therapy following major surgical intervention. -Temporary interruption of Nexavar therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. The decision to resume Nexavar therapy following a major surgical intervention should be based on clinical judgement of adequate wound healing.
Patients on Coumadin Anticoagulants / Warfarin co-administration	-Routine Pharmacovigilance activities.	-Warning in section 4.4 of the SPC that infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on Nexavar therapy. Patients taking concomitant Warfarin or phenprocoumon should be monitored regularly for changes in Prothrombin time, INR or clinical bleeding. -Statement in section 4.5 (interaction with other medical products) that INR should be checked regularly if Sorafenib is administered concomitantly with warfarin. -Abnormal prothrombin, INR listed in section 4.8 as ADRs
Hepatic impairment	-Routine Pharmacovigilance activities	-Warning in section 4.4 of the SPC that since Sorafenib is mainly eliminated *via* the hepatic route, exposure might be increased in patients with severe hepatic impairment No data are available for patients with Child Pugh C (severe) hepatic impairment. -4.2 Posology and method of administration also indicates that no data are available in Child Pugh C patients.
Elderly	-Routine Pharmacovigilance activities	-Warning in section 4.4 of the SPC that the experience with the use of Nexavar in elderly patients is limited and

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Potential Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		cases of renal failure have been reported. -Monitoring of renal function should be considered.
Safety in children	-A paediatric study to be run by the CTEP Children's Oncology Group in children with refractory solid tumours or refractory leukaemias is planned to start in second quarter 2006.	-Warning in section 4.2 of the SPC that Nexavar is not recommended for use in children and adolescents due to a lack of data on safety and efficacy. After repeated dosing to young and growing dogs, effects on bone and teeth were observed at exposures below the clinical exposure.
Pregnancy and lactation	-All reports of pregnancy occurring on Sorafenib reported to Bayer will be followed up with targeted questionnaires at appropriate intervals to record the outcome of the pregnancy and any adverse outcomes. Any congenital abnormalities will be recorded as SAEs and reported accordingly	-Warning in section 4.6 of the SPC (pregnancy and lactation) that Women of childbearing potential must use effective contraception during treatment. -Product labelling clearly states the harmful potential effects to a pregnancy if it occurs during Sorafenib dosing and the potential adverse effects Sorafenib may have on an ongoing pregnancy. -Contraindicated for breast-feeding women: Breast-feeding is contra-indicated during sorafenib treatment
Non-Caucasians	-Database of experience of Sorafenib in non-caucasian patients will be further expanded by additional data from non-Caucasian population studies conducted in Japan and Asia.	-Statement in section 5.2 of the SPC: *Race*: The mean sorafenib exposure was lower in Japanese patients than in Caucasian patients, but the exposure was highly variable. The clinical relevance of this observation is unknown.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.6 Overall conclusions, risk/benefit assessment and recommendation

Quality, Non-clinical pharmacology and toxicology

The quality of this product was considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

There were no issues concerning the quality, the non-clinical pharmacology or the toxicology of sorafenib that negatively affected the overall benefit-risk assessment. Some issues required further clarification, to be provided post-authorisation.

Efficacy

In a phase III, randomised, placebo-controlled trial, including patients with advanced clear cell renal cell carcinoma, with good performance status and without impaired organ function (half of the patients had an ECOG performance status of 0, and half of the patients were in the low risk MSKCC prognostic group), receiving sorafenib 400mg+best supportive care (BSC) or placebo+BSC twice daily as a second line therapy, the median time to progression or death was prolonged in the sorafenib group (167 vs. 84 days; $\alpha = 0.01$, two-sided p-value < 0.000001). These results corresponded to a 56% reduction in hazard over placebo.

A total of 903 patients were enrolled at the time of the survival analysis. Among them, 220 deaths were reported (123 in the placebo group, 97 in the sorafenib group). The hazard ratio was 0.72 ($p=0.018$). The survival analysis was non-significant. Survival data as of November 2005 were still considered immature (367 deaths in 903 patients). Formally the results were still statistically non-significant in relation to the stopping criteria for interim analyses. However, based on PFS data, it was concluded that a favourable and clinically meaningful effect had been demonstrated.

The analysis of an enrichment study design confirmed the activity of sorafenib in patients with advanced RCC and that the activity is mainly cytostatic.

Safety

During clinical trials, sorafenib was considered a well tolerated anti-cancer drug. Dermatological side effects and diarrhoea, and hypertension likely related to VEGF inhibition, were frequently observed and led to dose reductions and treatment withdrawal in some individuals. Neuropathy constitutes no major concern, and may be cumulative. There was a signal as regards pancreatitis. Further investigations will be conducted post-authorisation to understand the mechanism of hypophosphataemia.

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From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

Risk-benefit assessment

The antitumour activity of sorafenib was demonstrated in treatment-naïve and previously treated patients, irrespective of age, gender and Motzer prognostic criteria (good or intermediate risk). In terms of PFS, the results were statistically robust and median time to progression or death was prolonged with slightly less than 3 months. Two interim survival analyses were conducted (data cut-off May and November 2005). The hazard ratios in both analyses were about 0.75 (corresponding p-values of 0.015, i.e. nominally non-significant). The estimated median survival benefit was about 3+ months, i.e. a treatment effect considered clinically relevant. A final analysis of OS will be conducted when approximately 540 deaths are observed, but it is anticipated that the crossover of placebo patients from placebo to sorafenib arm after May 2005, limit interpretation of the results. However, after consultation of the oncology scientific advisory group (SAG), the CHMP considered that PFS *per se* could be considered as a measure of the clinical benefit of sorafenib. Based on PFS data, it was concluded that a favourable and clinically meaningful effect has been demonstrated.

Positive results are available (OS and PFS) from randomised trials using cytokines-based therapies in advanced RCC. Although several major questions remain about their application, cytokines-based therapies are widely used in Europe, and in the absence of comparative data relative to available treatment options, the oncology SAG did not recommend the use of sorafenib in first line, as initially proposed by the applicant. An ongoing, first-line, interferon alpha comparative study aiming at showing superiority in terms of PFS is ongoing.
Moreover, the applicant was asked to justify the proposed first line indication taking into account the study population of the pivotal study i.e., "second-line patients", low-moderate Motzer risk and clear cell carcinoma (mutation of the VHL gene). In retrospect and as no relationship between VHL mutation status and clinical outcome was identified, the indication was not restricted to clear cell RCC. In addition, acknowledging that patients with, e.g. an expected survival of less than 3 months are frequently excluded from clinical trials without restrictions of the indication, the CHMP did not consider it appropriate to restrict the indications to patients with poor prognosis according to Motzer score. The baseline disease characteristics of the population included in the pivotal study are mentioned in section 5.1 of the SPC. In line with the oncology SAG recommendations, the final wording adopted by the CHMP for section 4.1 of the SPC was: "*treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy". The* CHMP required a post-authorisation investigation of the activity of sorafenib in patients with papillary tumours through the conduct of an exploratory study utilising, e.g. effects on angiogenesis as outcome measure. Further post-authorisation exploratory biomarker studies were also required.
Based on available data, the benefit-risk balance of sorafenib was considered favourable, considering the relatively positive safety profile of this medicinal product. The benefit-risk assessment was strengthened by immature survival data (HR 0.7, p=0.02). However, it was acknowledged that the assessment of the full potential of sorafenib in terms of survival benefit in the treatment of advanced RCC would not be possible due to the early unblinding of study results and subsequent cross-over. Due to the availability of active authorised treatment for the first-line treatment of advanced renal cell carcinoma RCC, the indication was restricted to use in second-line.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

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Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Nexavar in the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy was favourable and therefore recommended the granting of the marketing authorisation

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